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(54) Title: BENZOPYRAN DERIVATIVES HAVING LEUKOTRIENE-ANTAGONISTIC ACTION

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7) Abstract

The present invention relates to novel benzopyran derivatives of formula (I), wherein A is an oxygen or sulfur atom or a methylene out; B and C are: a) when B is a benzofused heterocycle (a) wherein U is an O, S or N atom, Z-Y are two carbon atoms linked by a suble or single bond and T is a single bond, a methylene or carbonyl group, C can be a -CONR⁷-, CSNR⁷-, -SO₂NR⁷-, -CH₂O-, -CH₂O-, oup; b) when B is a phenyl group (b), C can be a -SO₂NR⁷-, -CH₂O-, -CH₂CH- group; D is a 5-tetrazolyl or -COOR⁸ group, wherein R⁸ is vdrogen, a (C₁-C₄)-alkyl or phenylalkyl group; and m and n are integers between 0 and 4. Said compounds show a leukotriene-antagonistic citivity, and they are valuable as anti-inflammatory and antiallergic medicaments or in the treatment of cardiovascular diseases.

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BENZOPYRAN DERIVATIVES HAVING LEUKOTRIENE-ANTAGONISTIC ACTION

and preparation of the novel benzopyran benzopyran antagonistic compositions salts derivatives as well as to the therapeutic use thereof activity. The present invention also relates acceptable relates to novel containing them, having a leukotriene thereof and pharmaceutical derivatives, the pharmaceutically invention TECHNOLOGICAL BACKGROUND process for the The present solvates

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acid (AA), which related compounds fundamentally esterifies the hydroxyl at the 2- position eicosanoids, of the glycerol of the phospholipids contained in the cell membranes. AA is released from the phospholipid containing it by the action of a lipase, phospholipase A_2 (PLA $_2$) ("CRC Handbook of Eicosanoids and Related Florida (1989)). After being released AA is metabolized in mammals mainly by two different pathways or enzyme produces significant the of Clinical Research, are also involved in inflammatory reactions, exhibiting directly involved and 20 carbons Lipids", vol. II, Ed. A.L.Willis, CRS Press peptide-leukotrienes $\mathtt{LTC_4}$, $\mathtt{LTD_4}$ and $\mathtt{LTE_4}$. All leukotrienes, the most important being \mathtt{LTB}_4 , Through lipoxygenase it LL In. prostaglandins and thromboxanes, the most most cyclooxygenase acid having well known that arachidonic and inflammation (Higgs et al. Annals being PGE_2 and TxA_2 , which are leukotrienes fatty called Through 287 (1984)). prostaglandins, from a unsaturations, S

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LTB4 (1991)). It has been widely shown that LTC_4 and LTD_4 have strong constrictive action on human bronchi (Dahlen (Bailey and Casey, subsequent production (Marom et al., Am. Rev. Resp. Dis., 126, 449 mucus cardiopathy. This relationship has been confirmed by the bronchial asthma, chronic bronchitis, allergic rhinitis, vascular 80, 497 diseases effects, together with the strong contractions observed that these mediators might contribute to other cardiovascular On the other hand, anaphylaxis degranulation. (Salmon et al., Prog. Drug Res., 32, role thus involved in the pathogenesis secretion 203 (1982)). Leukotriene tissue caused by LTC_4 and LTD_4 , suggest they 33, 521A (1985)). and Br. J. Pharmacol., important and are involved in some inflammatory arteries can produce these about of the increase of inflammation observed; their peptide-leukotrienes heart the which 484 (1980)), bring pathogenesis hypersensitivity reactions stimulating and psoriasis. coronary spasm, playing an of leukocytes and agent cardiovascular system have been cerebral oedema and endotoxic shock. also (Piomelli et al., J. Clin. Res., the λq al., chemotactic Peptide-leukotrienes Chem., 11, caused by 288, airways mainly involved in the chemotactic activities, and permeability (Camp et есхеша Of Nature, SI enzymes fact that coronary effects obstruction of such being Rep. Med. atopic a strong extravasation infiltration immediate lysosomic (1982)), in heart (1883)) several et et

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said above it follows that the control From what

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have been described the present invention, having moreover as al. N-[4-oxo-2-(1H-5-tetrazolyl)-4H-1-benzopyran-8-yl]-4-(4-phenylbutoxy)benzamide and the derivatives thereof (EP 173,516) as strong leukotriene antagonists. All these derivatives have an amide or thioamide group other functional groups as bridges and polar moieties, can have being not of al. On the other hand, the derivatives of the present invention show the advantage of a very high oral a lipophilic moiety. present and/or the patent as structurally related to et acid Ï the metabolic amides as well, in any case such derivatives Toda in a bridge between an included within the general formula of containing disclosed on leukotrienes. their compounds to compounds carbocycle between other lipophilic In literature some considered structure as thanks invention, besides action chemical stability. the Therefore, the bioavailability moiety and a of can be inhibitory described compounds their et ij

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are On the other hand, Huang F. C. et al. (US 4977162 as potent 4-0x0-7-[[3-(2thioethers, quinolinylmethoxy) phenyl] methyloxy]-2-(1H-5-tetrazolyl)compounds thereof ethers, said derivatives described of containing All leukotriene antagonists. the 5082849) derivatives and 4H-1-benzopyran quinoline

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compounds general formulae, which quinoline heterocycle heterocycle is never present in the general formulae that vinylenes the present invention in such the lipophilic moiety. Therefore chromane ketones, acid function and quinoline within their bridges between the claims of the present invention. amides, sulfones, of an from those with sulfoxides, containing equivalent amines as contain a

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high the to now. The present invention exhibit compounds with problem good Show that that and an unresolved in therapy compounds action, activity obtention of are useful antagonistic novel still antagonistic antagonists up series of and .H However, the mentioned adsoprtion bioavailability leukotriene ದ number of provides above

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DISCLOSURE OF THE INVENTION

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benzopyran provides novel derivatives of general formula I invention The present

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wherein:

- a methylene group; atom or sulfur is an oxygen or ~
- can be:
- a) a benzofused heterocycl

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00

wherein:

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the wherein R^5 is hydrogen or (c_1-c_4) -alkyl, the R^5 substituent containing A when said substituent is the 1- position of the benzofused oxygen or sulfur atom or a NR⁵ group þý group being optionally substituted heterocycle; an bound to

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carbon atoms linked together by a single bond or by a double bond; represent two and Y

H

or - T is a single bond, a methylene group group; carbonyl

wherein:

- the substituent containing A is bound to any one the of position or 4-2-, 3benzofused heterocycle; of the possible 1-,

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- the substituent containing C is bound to the 6or 7- position of the benzofused heterocycle;

b) a phenyl group

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to is bound the phenyl group at the 3-, 4- or 5- position; wherein the substituent containing C

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is a diradical which represents: U

-CONR7-, wherein group, benzofused heterocycle, a -CH=CH--CH₂O-, R7 is hydrogen or methyl; -SO2NR7-, is a m -CSNR7-, a) when

group, a -50_2NR^7 -, $-CH_20$ -, -CH=CH- group, wherein R^7 is hydrogen or methyl; phenyl ಥ Bis b) when

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less -COOR8 group, wherein R8 a phenylalkyl group of hydrogen, a (C_1-C_4) -alkyl or is a 5-tetrazolyl or than 10 carbon atoms; Д

hydrogen, independently ; HOare -OCH₃ or and Re halogen, (C_1-C_4) -alkyl, R1, R2, R3, R4

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m and n are integers from 0 to

for the novel benzopyran derivatives, provides a process use thereof. also The present invention as the therapeutic preparation of well

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the The present invention also relates to the solvates Of the salts particularly pharmaceutically acceptable and H represented by formula Ia, formula of compounds the and

Ia

+ ≥

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amount of an alkaline-earth metal deriving ethanolammonium, wherein M+ is an alkali metal cation (e.g. Na+, K+), a cation salt (e.g. $1/2 \text{ Mg}^{2+}$), or ammonium Ca2+, represents the half an amine or 1/2 cation (e.g. from

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diethanolammonium, triethanolammonium, tris(hydroxymethyl)methylammonium).

more iQ rd present stereoisomers O one The can have structure. possible of formula their the well as the mixtures thereof. a11 ri Li invention comprises carbons compounds

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Preferred compounds are those wherein $\rm R^1$ and $\rm R^2$ are hydrogen, fluorine or chlorine and D is a 5-tetrazolyl or $\rm COOR^8$ group, wherein $\rm R^8$ is hydrogen, methyl, ethyl or benzyl.

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Preferred compounds also are those wherein B is a benzofused heterocycle and C is a $-\text{CO-NR}^7-\text{ or }-\text{CH-GH-group}.$

Further preferred compounds are those of general formula I wherein B is a phenyl group and C is a -CH=CH-, -CH $_2$ O- or -SO $_2$ NR 7 - group.

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ď the compounds of formula is H 0 to 2, B is a carbon the substituent benzofused heterocycle and the substituent containing A the benzofused a single bond or -CO-NR7a NR⁵ group, wherein R⁵ can be substituted by of benzofused heterocycle wherein Y-2 represents two position Ø and wherein the m and n are integers from 1 is hydrogen or methyl, C is position of -9 atoms linked by a double bond, T is Particularly preferred are the the C is bound to 1- or 2substituent containing A, group and U is Or methyl to the -CH=CH- group, wherein R³ or containing ponuq carbonyl

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Particularly preferred also are the compounds of formula I wherein $\rm R^3$ is hydrogen, $\rm R^4$ is hydrogen, fluorine, chlorine, methyl or methoxide, C is a -CONR⁷-

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oxygen substituent containing C is bound the benzofused heterocycle and the numberings double bond, M position represents ò U is an 40 the from 1 2 ๗ and the 40 Z - Xcarbon atoms linked by a single bond or integers single bond or a methylene group according bound to wherein are ထ substituent containing A is the benzofused heterocycle benzofused heterocycle and n the position of E wherein -CH=CH- group, described above. and to the 6-S

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O containing respective -CH20compounds ന -CH=CH-, a phenyl group in which the substituents are linked to the phenyl group at the 0, m is an integer from are the æ D. also U preferred wherein relative para position. group, n is formula I Particularly -SOZNR7and C general B is ~

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Most preferred compounds of formula I of the present invention are the following ones:

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8-[2-(benzyloxymethyl)chromane-6-carboxamido]-4-oxo-4H-1-benzopyran-2-carboxylic acid;

N-[4-oxo-2-(1H-5-tetrazolyl)-4H-1-benzopyran-8-yl]-2-(benzyloxymethyl)chromane-6-carboxamide;

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8-[2-(3-phenylpropyl)chromane-6-carboxamido]-4-oxo-4H-1-benzopyran-2-carboxylic acid;

N-[4-oxo-2-(1H-5-tetrazoly1)-4H-1-benzopyran-8-y1]-2-(3phenylpropy1)chromane-6-carboxamide;

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8-[2-(benzyloxymethyl)benzofuran-5-carboxamido]-4-oxo-4H-1-benzopyran-2-carboxylic acid;

8-(2-benzyloxymethyl-2,3-dihydrobenzofuran-5-carboxami-do)-4-oxo-4H-1-benzopyran-2-carboxylic acid;

30 N-[4-oxo-2-(1H-5-tetrazolyl)-4H-1-benzopyran-8-yl]-2-benzyloxymethyl-2,3-dihydrobenzofuran-5-carboxamide;

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8-[2-(3-phenylpropyl)-2,3-dihydrobenzofuran-5-carboxamido]-4-oxo-4H-1-benzopyran-2-carboxylic acid;

N-[4-oxo-2-(1H-5-tetrazoly1)-4H-1-benzopyran-8-y1]-2-(3-phenylpropy1)-2,3-dihydrobenzofuran-5-carboxamide;

8-(2-benzylthiomethyl-2,3-dihydrobenzofuran-5-carboxami-do)-4-oxo-4*H*-1-benzopyran-2-carboxylic acid;

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8-[2-(4'-fluorobenzyloxymethyl)-2,3-dihydrobenzofuran-5-carboxamido]-4-oxo-4H-1-benzopyran-2-carboxylic acid;

N-[4-0x0-2-(1H-5-tetrazoly1)-4H-1-benzopyran-8-y1]-210 (4'-fluorobenzyloxymethyl)-2,3-dihydrobenzofuran-5-carboxamide;

8-[7-chloro-2-(3-phenylpropyl)-2,3-dihydrobenzofuran-5-carboxamido]-4-oxo-4H-1-benzopyran-2-carboxylic acid;
8-[2-(3-phenylpropyl)-2,3-dihydrobenzofuran-5-carboxami-

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do]-6-fluoro-4-oxo-4H-1-benzopyran-2-carboxylic acid; 8-[4-chloro-2-(3-phenylpropyl)-2,3-dihydrobenzofuran-5carboxamido]-4-oxo-4H-1-benzopyran-2-carboxylic acid; 8-[6-chloro-2-(3-phenylpropyl)-2,3-dihydrobenzofuran-5-

carboxamido]-4-oxo-4H-1-benzopyran-2-carboxylic acid;
20 N-[4-oxo-2-(1H-5-tetrazolyl)-4H-1-benzopyran-8-yl]-1-(4-phenylbutyl)-3-methylindole-5-carboxamide;

8-[[4-(4-phenylbutoxy)phenyl]methyloxy]-4-oxo-4H-1-ben-zopyran-2-carboxylic acid;

8-[[4-(4-phenylbutoxy)phenyl]sulfonylamino]-4-oxo-4H-1-benzopyran-2-carboxylic acid;

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8-[(E)-2-[4-(4-phenylbutoxy)phenyl]ethen-1-yl]-4-oxo-4H-1-benzopyran-2-carboxylic acid;

8-[(B)-2-[4-(4-phenylbutoxy)phenyl]ethen-1-yl]-4-oxo-2-(5-1H-tetrazolyl)-4H-1-benzopyran;

8-[(B)-2-[4-[4-(4-fluorophenyl)butoxy]phenyl]ethen-1

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yl]-4-oxo-4H-1-benzopyran-2-carboxylic acid;

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8-[(E)-2-[4-[4-(4-fluorophenyl)butoxy]phenyl]ethen-1-yl]-4-oxo-2-(5-1H-tetrazolyl)-4H-1-benzopyran;
8-[(E)-2-[4-(4-phenylbutoxy)-2-fluorophenyl]ethen-1-yl]-

8-[(E)-2-[2-(4'-fluorobenzyloxymethyl)-2,3-dihydroben-zofuran-5-yl]ethen-1-yl]-4-oxo-4H-1-benzopyran-2-carboxylic acid;

acid;

4-oxo-4H-1-benzopyran-2-carboxylic

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8-[(E)-2-[2-(4'-fluorobenzyloxymethyl)-2,3-dihydrobenzo-furan-5-yl]ethen-1-yl]-4-oxo-2-(5-1H-tetrazolyl)-4H-1-

10 benzopyran;

8-[(E)-2-[4-[4-(4-chlorophenyl)butoxy]phenyl]ethen-1-yl]-4-oxo-2-(5-1H-tetrazolyl)-4H-1-benzopyran;
8-[(E)-2-[4-[4-(4-methylphenyl)butoxy]phenyl]ethen-1-yl]-4-oxo-2-(5-1H-tetrazolyl)-4H-1-benzopyran;

8-[(E)-2-[4-[4-(4-methoxyphenyl)butoxy]phenyl]ethen-1-yl]-4-oxo-2-(5-1*H*-tetrazolyl)-4*H*-1-benzopyran;
8-[(E)-2-[4-[4-[4-(iso-propyl)phenyl]butoxy]phenyl]-ethen-1-yl]-4-oxo-2-(5-1*H*-tetrazolyl)-4*H*-1-benzopyran;
8-[(E)-2-[4-[4-[4-(tert-butyl)phenyl]butoxy]phenyl]-

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20 ethen-1-yl]-4-oxo-2-(5-1H-tetrazolyl)-4H-1-benzopyran; 8-[(E)-2-[4-[4-(4-chlorophenyl)propyloxy]phenyl]ethen-1 yl]-4-oxo-2-(5-1H-tetrazolyl)-4H-1-benzopyran; 8-[(E)-2-[4-[4-(4-fluorophenyl)propyloxy]phenyl]ethen-1 yl]-4-oxo-2-(5-1H-tetrazolyl)-4H-1-benzopyran; 8-[(E)-2-[4-[4-(4-methylphenyl)propyloxy]phenyl]ethen-1-yl]-4-oxo-2-(5-1H-tetrazolyl)-4H-1-benzopyran;
8-[(E)-2-[4-[4-(4-methoxyphenyl)propyloxy]phenyl]ethen-1-yl]-4-oxo-2-(5-1H-tetrazolyl)-4H-1-benzopyran;

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8-[(E)-2-[4-[4-[4-(iso-propyl)phenyl]propyloxy]phenyl]-ethen-1-yl]-4-oxo-2-(5-1H-tetrazolyl)-4H-1-benzopyran;
8-[(E)-2-[4-[4-[4-(tert-butyl)phenyl]propyloxy]phenyl]-

r-1

ethen-1-yl]-4-oxo-2-(5-1H-tetrazolyl)-4H-1-benzopyran; as well as the carboxylic acid esters described in the examples.

According to the present invention, the compounds of general formula I are obtained through one of the following processes:

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a) when in general formula I D is $-\text{COOR}^8$, a starting compound of general formula II,

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II

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wherein R^1 , R^2 , A, B, C, m and n have the above mentioned meanings, is reacted with a commercial compound III,

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III

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the O. AS suitable organic O mixtures thereof, at a temperature ranging from 50° to a time between 3 and 18 hours. The resulting hydrogen, in the presence of a metal alkoxide such exception tetrahydrofuran of. alcohol with the the conjugated sodium methoxide or ethoxide, in corresponding base, ethyl ether, wherein \mathbb{R}^9 is the residue \mathbb{R}^8 S S such compound IV, 85°C for solvent

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ΛI

is subjected to a treatment with concentrated or diluted hydrochloric acid in a suitable solvent such as ethanol, methanol, tetrahydrofuran or mixtures thereof, at a temperature ranging from 25°C to the solvent reflux, for a time between 1 and 24 hours, to obtain compound V,

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the sodium or potassium organic a temperature ranging between 0°C and the solvent reflux hydrolysis by treatment with which coincides with I wherein D is COOR8 or, when D solvent such as methanol, ethanol or tetrahydrofuran, converted into I removing suitable M i i lithium, a time from 30 min to 18 hours. aqueous solution as through alkali S) such formula I, suitable base, hydroxide, in 디 COOH for

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b) when in general formula I D is the 5-tetrazolyl group, a starting compound of formula VI,

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VI

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above the OI solvent such as ranging between to 24 hours, such as ammonium chloride mentioned meanings, is reacted with sodium azide in the have from 1 in a suitable temperature G and a time thereby obtaining the compound VII, E ບັ 25° and solvent reflux, for rti acid N, N-dimethylformamide, at Pyridinium hydrochloride, M ¥ a mild wherein R1, R2, of presence

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is the Ω coincides with I wherein which group.

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5-tetrazolyl

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c) In an alternative process for the preparation of a compound of general formula I wherein C is -CO-NR7-, starting compound VIII,

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VIII

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above mentioned the meanings, is reacted with a compound IX, n have and E m a. wherein R1,

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and when D in from protecting group, for example a methyl, ethyl or benzyl is carried out carboxychloroform, methylene temperature excess at pyridine, in wherein \mathbb{R}^2 and \mathbb{R}^7 have the above mentioned meanings of a base such a time from 3 to reacting a time suitable ø or, previously preparing the acid chloride of and 80°C for subsequently Œ chloride in I hours. The resulting compound of formula X, triethylamine, 4-dimethylaminopyridine or ester. The reaction between VIII and IX at is COOH, then E contains a with a compound IX in the presence group D N, N-dimethylformamide, ranging between 0° and 40°C and for such as oxalyl temperature ranging between 50. hours and the an an solvent to by reaction with equivalent 30 minutes to 1,5 aprotic OT formula I can be suitable chloride VIII 15

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any is for ethyl ester, it can be removed by alkali hydrolysis as described above for the preparation 07 converted into I wherein C is -CONR7- by removing M -CONR7-COOH-protecting groups present in E, thus, when U I wherein D=COOH starting from V. wherein with I a methyl or which coincides example

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starting a compound rd a process for the preparation of $-cH_{2}^{0-}$, is ပ wherein compound of formula XI, general formula I d) In of

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XI

above mentioned with bromine atom or reacted the 1.5 and n have chlorine or group, aryl-sulfonate E rd (N |---| B meanings and X wherein R¹, A, compound XII or alky1-

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M)

XII

have the above mentioned meanings, in temperature ranging between 25° and 80°C for a time from metal hydroxide, such 5 to 48 hours. The resulting compound of formula XIII N, N-dimethylformamide solvent a suitable **a**S a such carbonate in base methanol or ď and E of presence OH wherein R² alkoxide ethanol,

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XIII

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alkali hydrolysis as described above for the preparation ethyl ester, it can be removed by C is -CH20- by removing any for COOH-protecting groups present in E, thus, when E is -CH₂0-, S ပ of I wherein D=COOH starting from V. wherein wherein which coincides with I example a methyl or converted into I

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formula I wherein C is $-50_2 \mathrm{NR}^7-$ and A is oxygen compound of æ of e) In a process of preparation sulfur, a starting compound XIV, general

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S

XIV

wherein \mathbb{R}^2 , \mathbb{R}^7 , \mathbb{B} , \mathbb{E} and \mathbb{n} have the above mentioned meanings and \mathbb{A} is an oxygen or sulfur atom, is reacted with a compound x_V ,

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X

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out base suitable for the pk_a of the alcohol or thiol, such wherein \mathbb{R}^1 , X and m have the above mentioned meanings. of XIV by reaction with a and resulting carbonate such as N,N-dimethylformamide tetrahydrofuran at a temperature ranging between 25° carried The as a metal hydride, alkoxide, hydroxide or S) hours. AX pue 8 previously preparing the salt to C between XIV ~ from solvent time reaction N compound XVI suitable for D.08

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XVI

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oxygen or sulfur by removing any COOHremoved by into I wherein C E IS and as described for the preparation -SO2NR7thus, when D. can S 는 다 converted U ester, in B, Wherein wherein D=COOH starting from V. ethyl groups present sulfur, or is coincides with 0 -SO2NR7- and A is alkali hydrolysis example a methyl protecting or oxygen which

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the in 37, O from the compounds with of general formula I wherein treatment Tetrahedron, conditions -conr7- by al., starting the et JS in (Clausen K. obtained compounds wherein A reactive are The literature Lawesson's formula I -CSNR7-(4 3635).

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ion the pe mixtures tris(hydroxymemin to can formula Ia base or to for example, I according such as from 15 25. ៧ between can be treated with general or of water-methanol or ethanol for a time suitable solvent this purpose, hydroxide temperature ranging of chemical methods. Thus, specific salt sodium exchanger suited for desired, a compound I w thyl)methylamine in solvent reflux. with ದ ιΩ hours, at When treated 75 20

A starting compound of formula VI can be obtained starting from a compound of formula V through the Process shown in scheme 1.

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Scheme 1

M

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N2N-C

75

$$R^{1}$$
 R^{1}
 CH_{2}
 MC
 NC
 NC

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a temperature ranging between with can be obtained by such example solvent for carboxamide XVII, In this sequence, a compound VI Ø oxychloride, in N, N-dimethylformamide, at a rd of dehydration phosphorous

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The treatment with gaseous ammonia temperature ethanol, time from 15 minutes of a time from 3 to 24 hours (step 2). aminolysis such as methanol, rd thereof, at obtained by rcs ranging from -30° to 25°C, for a mixture 20 solvent XVII can be example, by or 24 hours (step 1). 0 and 50°C, for suitable tetrahydrofuran ester V, for carboxamide Ø

A starting compound of formula IIa, i.e. of general formula II wherein C is $-CO-NR^7-$, can be obtained, for example, by reaction of a compound VIII with a compound XVIII,

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XVIII

TO

wherein R^2 and R^7 have the above mentioned meanings, 20 following the same process as described for the preparation of compound X starting from VIII and IX.

of De in I Shown can -CH=CH-, process IIb, formula C is example, through the of formula II wherein starting compound for obtained, general ~ scheme

Scheme 2

XIX
(3)
(CH₂)_m—A—(CH₂)_n—B—CH=CH₂

M

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 $(CH_2)_m - A - (CH_2)_n - B - C$ + A + A

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in XX can be an such as tetrahydrofuran or ethyl ether, at suitable base such as butyl lithium, a temperature ranging between 0° and 25°C and for a time 0 reaction between compound XIX and a commercial methylphosphonium salt or lithium bis(trimethylsilyl)amide in compound 3 starting by Wittig from 45 minutes to 36 hours (step IID rd example, sequence, N of for this inert solvent sodium amide the presence obtained, In

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A compound IIb can be obtained by reaction of a compound XX with a compound XXI in the general

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olefins of palladium (II) acetate and triethylamine the reaction). and XXI is carried out acetonitrile, at of complexes (Heck insertion temperature of the solvent reflux and for O.f as Then, the reaction between XX conditions for the reaction such catalyzed by palladium (0) suitable solvent to 48 hours (step 4). the presence

M

A starting compound of formula VIIIa, i.e. of general formula VIII wherein B is a benzofused heterocycle

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group is bound to the benzene ring at the para position example, starting mentioned T and n have the -COOH COOR9, wherein R9 above, following any the synthetic processes represented in scheme 3. Y-Z and T have the above an oxygen or sulfur atom and ø Y-Z, **S** Ö for from a compound XXII, wherein R3, R4, group above mentioned meanings and can be obtained, represents the groups defined chlorine, bromine atom or a R4 to the U atom, meanings, U is wherein R³,

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T. XXIII COOH TIO-(CH₂)," G = CI, Br 6 (CH2)m-M S (CH₂)_m-A-(CH₂)_n Scheme 5 CHO Cal O (10)when XXII (9)

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compound 9 easily available through sulfonate from with hydride oxygen, represent represents time 7. 1. W such as i S ≪ or aryl-Ø subjecting subsequently reacting is, when A is tetrahydrofuran, sodium temperature ranging between 0° and 25°C, for compound XXV with defined above and U q Processes, wherein R1 and organic solvent a base such as bromine or chlorine atom or an alkyl-E for example, T, Y-Z, G, or Σ and commercial 01 groups and the values sednence potassium hydride and 3 to 24 hours (step 6). action of defined above A CH in a suitable obtained, N, N-dimethylformamide ж Э chemical XXIV, this XXII to the R1, sulfur, is compound III similar group, groups

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compound XXIII, wherein and obtained, base such as potassium (thio1), chemical 40 sodium ethoxide, in mentioned meanings at 4 represents the trifluoromethanesulfonate group, from easily available through similar group A compound XXV wherein A is sulfur can be N, N-dimethylformamide, time ethanol, SH for an 25°C, and n have the above :C processes, in the presence of a methoxide or S S Ø of Σ such example, by reaction compound XXIV wherein . or o.f temperature ranging solvent sodium 24 hours (step 7). dimethylsulfoxide commercial or Q hydroxide, R4 suitable Tfo E A

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C) hr suitable meanings, with methylene group a compound XXIII, wherein in a in the salt, a MgBr group, mentioned ൯ (I) compound XXV wherein A is copper above 5 ന ot of compound XXIV where M R^4 , G and n have the reaction catalytic amounts obtained by

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VIIIa

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bromide for 24 hours (step 7). A compound XXIV with and the solvent reflux and for established or tetrahydrofuran, commercial and magnesium, following the processes ๗ the preparation of Grignard reagents. from ether obtained starting temperature between 0°C as ethyl time from 2 to such MgBr is solvent

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A compound XXIII is obtained starting from a compound XXII by reaction with trifluoromethanesulfonic anhydride in the presence of pyridine or triethylamine in methylene chloride, at a temperature between -10° and 25°C and for a time from 4 to 24 hours (step 5).

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A compound VIIIa can be obtained starting from XXV with G equal to the group COOR⁹ (step 8) through alkali hydrolysis as described for the preparation of I with D = COOH starting from V.

(2) (2)

with the A compound VIIIa can be obtained starting from XXV is hydrogen, subjecting it to the conditions subsequently of obtained by oxychloride in N,Nsulfuric acid and time from 1 and 25°C and for a time from 4 to ø 24 hours allows to obtain the compound VIIIa (step 10). acetone at for example, at to XXVI XXVI N-methylformanilide of Jones reagent. A compound XXVI is thus and for a and **a** 9). The treatment corresponding carboxylic acid by means, aldehyde chromium trioxide in the presence of suitable solvent such reaction with phosphorous temperature between 25° and 100°C resulting Vilsmeier-Haack or temperature between 0. to 24 hours (step dimethylformamide XXV the of in a Ö oxidizing wherein the of

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A compound VIIIa can also be obtained starting from XXV wherein G is chlorine or bromine by substitution of

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atom high-boiling order in which compound potassium temperature between 25. hours 11). Alternatively, a compound XXVII where conditions bromine reaction carboxylic ρχ from to Ŋ from XXVII 9 ū and Finally, O N time suitable as N-methylpyrrolidinone, at the is obtained by sodium such reversing the chlorine group to reaction group in ಗ solvent out. 230°C, for of obtained starting ๙ in the presence ĸ ៧ a t carried nitrile nitrile (C) and the solvent reflux for Braun suitable (I) cyanide compound XXVII obtained dioxane O 150° to compound XXV wherein 11 are the halogen with a the Rosenmund-von tetrahydrofuran or is oxygen can be Ø r. of can be in ranging from and such copper (step Ø hydrolysis hydrolysis (step 12). Thereby, ယ solvent VIIIa steps

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A starting compound of formula VIIIb,

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VIIIb

i.e. of general formula VIII wherein B is a benzofused heterocycle

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wherein \mathbb{R}^3 , \mathbb{R}^4 , Y-Z and T have the above mentioned meanings, U is an oxygen or sulfur atom and the -COOH benzofused a compound group is bound to the 7- position of the starting from heterocycle, can be obtained 27 XXVIII

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wherein G is a chlorine or bromine atom, following the the according to described for preparation of VIIIa starting from XXV that ខ្ល process steps (11) and (12). same synthetic

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XXVIII can be obtained formula starting from a compound XXIX, compound of

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XXXX

wherein R^3 , R^4 , T, Y-Z and n have the above mentioned through one of the synthetic processes described above for the preparation of XXV starting from OH meanings, U is oxygen or sulfur and G is a chlorine atom,

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of general formula VIII where B is a benzofused heterocycle i.e. starting compound of formula VIIIc,

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is a nitrogen atom N-substituted with the CH=CH, $m R^{1}$, $m R^{3}$, $m R^{4}$, A, m and n have the above mentioned substituent containing A, T is a single bond and Y-Z is meanings and \mathbb{R}^3 is a $(\mathbb{C}_1^-\mathbb{C}_4)$ -alkyl at the 3- position of the heterocycle, can be obtained, for example, following the synthetic sequence shown in scheme 4. wherein U

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following be obtained (step 14) for described XXX obtained established synthetic processes (step 13). compound conditions usually compound XXXI pe commercial can Vilsmeier-Haack reaction. XXXII In this sequence æ formylation in the ot compound esterification

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of compound XXXIV can be obtained by N-alkylation compound XXXIII, commercial such 25. such temperature between solvent 100°C, for a time from 2 to 24 hours (step 15). group chemical suitable suitable leaving chlorine or bromine atom or an alkylsimilar Ŋ tert-butoxide, in a good of Ø through N, N-dimethylformamide, at group, in the presence XXXII with a T. œ available Wherein compound potassium tions,

is methyl is obtained by example, with sodium cyanoborohydride in the presence of compound XXXIV (step ργ out, suitable phosphonium solvent is a (C_1-C_4) -alkyl carried between 25° and 90°C and for a time from 1 hydrogenolysis under hydrogen atmosphere in group can be in a suitable at solvent, pe reduction of the formyl group of a the can A compound XXXV wherein R³ suitable the methyl and wherein R³ oť ಹ transformation palladium catalyst with reduction rd reaction i, from compound XXXV zinc iodide followed by Said different

VIIIc can be obtained starting from XXXV described for I with D=COOH starting from V (step 17) through alkali hydrolysis compound preparation of

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COOH₉

(PT)

(91)

IIXXX

VIXXX

VIIIC

S

OHC'

IXXX

Зсуеше ₹

(LT)

20

(13)

IIIXXX

(SI)

HOOD

XXX

AXXX

32

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benzofused 31 compound of formula VIIId, Ø m wherein VIII formula starting heterocycle general

of

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wherein U is a NR^5 group, T is a carbonyl group and Y-Z is a CH=CH group, \mathbb{R}^3 is hydrogen, \mathbb{R}^5 is a $(\mathbb{C}_1-\mathbb{C}_4)$ -alkyl and the values defined above, can be obtained, for example, following the synthetic sequence shown in scheme 5. and R^1 , R^2 , X, m and n represent the groups

XI

IIIAXXX IAXXX

gcyeme 2

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followed by methylation with corresponding bromide following preparation a compound XXXVI literature. A compound XXXVIII is obtained by reagent XXXVII, according by reaction of the In this synthetic sequence for XXXVI with a Grignard organomagnesium compounds, methyl iodide according established starting from the carbon easily acid with

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(21)

temperature compound example, in the preparation of I with D=COOH starting compound XXXIX allows to prepare the 4-quinolone a suitable base such (step 19). A compound XLI is obtained by N-alkylation from V, allows to prepare a compound VIIId (step 21). from XXIII (step 18). The reaction of XXXVIII solvent described for the preparation of XXV with $A=CH_2$ Ø and 100°C and for a time from 4 described sodium or potassium hydride, in a suitable as N,N-dimethylformamide or benzene, at hydrolysis the processes a compound XL in the presence of alkali XLI according to between 0. 10 15 20

o.f

A starting compound of formula VIIIe

PIIIA

XIL

2

VIIIe

positions with i.e. of general formula VIII wherein B is a phenyl its free of one any substituted at

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- confruned

35 group, can be prepared starting from a compound XLII

XLII

the chemical mentioned (K=CHO), for easily available through similar following one of the synthetic processes used group above a formyl the preparation of VIIIa starting from XXII. and n have or and K can be G processes, wherein R⁶ commercial or meanings

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step and from Specifically, when n is 0, a compound VIIIe can be chemical methods, with a compound XXIV wherein M the Mitsunobu reaction; i.e. by reaction of XLII (with n=0) with XXIV (with M=OH) in the presence of diethyl azodicarboxylate solvent such as time from the Mitsunobu reaction carbonate XXIV such 0-alkylation reaction, a chlorine or bromine atom or an alkyl- or second wherein n=0 as N, N-dimethylformamide at a temperature between 0. first starting solvent compound the subjecting a compound XLII with n=0 and K=COOR9 tetrahydrofuran at room temperature and for a action of a base such as a metal hydroxide or The In aryl- sulfonate group in a suitable organic commercial or easily available conditions of involves the reaction of a compound XLII 24 hours. subsequently reacting it with a process. triphenylphosphine in a suitable a Williamson hours. Alternatively, a two-step a time from 2 to general can be replaced by following the () -H ä 100°C, for 72 prepared k=COOR9, wherein M similar and

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step, compound VIIIe is obtained by hydrolysis of the ester obtained in the preceding step, following the process described for the preparation of I with D=COOH starting from V.

The starting compounds XI and XIX can be obtained, for example, following the synthetic processes shown in scheme 6.

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K)

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with ranging from 25°C to the solvent reflux for a time from (step 22). A compound XI wherein X is XLIII following chemical processes widely described in can be prepared HO compound reaction with pyridinium þ is prepared starting a temperature between inert compound XLII with K=CHO (formyl) with (step 23). 24). Alternatively, suitable solvent such alkylobtained as dichloromethane at room temperature or in example, dioxide in an borane in an inert ro following one of the processes example mesyl the solvent, oxidizing 24 hours oxygen can be p t with for compound XLIII ethyl ether or tetrahydrofuran VIII, reaction a t to sulfonate group compound XIX can be obtained by with manganese a time from 2 to 24 hours (step for a time from 8 Œ compound pyridine as dichloromethane example, by or presence of triethylamine in compound XIX wherein A is chloride, XLIII by aluminium hydride sequence, a preparation LQ. chlorochromate or for 0. compound alkyl- or arylliterature, for using aryl- sulfonate 2 to 24 hours XXIV Ø reduction and 25°C chloroform or such this reaction of chloride, compound such as lithium ಥ solvent

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XIX

JM-A-(CHJ)-B-CHO

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prepared following the synthetic process represented in scheme 7. general formula XIV wherein E is -COOR9, can be starting compound of formula XLVII, 25

of

XLII

from

starting

VIIIe

of

XXIV.

IX

Sm-A-(CHSn-B-CH2X (EZ) XFIII Sym-A-(CH2h-B-CH2OH (24) (22) IIIV

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асуеше е

99

above for the preparation of V boron tribromide in a solvent such as dichloromethane or ethyl ether at a temperature ranging from -40°C to the compound XLIV, wherein B and and XVIII, conditions described transformation is effected by treatment cleavage of treatment with hydrochloric acid hydroxyand R10 preparation of IIa starting from VIII 27) group, is A compound XLVI with << when B 26). The meanings, suitable (step group, n=0 XLV compound XVIII (step 25) in the protecting group, for example, XLVI a methyl compound ര (step mentioned a phenyl in to the process described XLV. R10 R10 n=0, R10 can be ιΩ from II compound protecting group and XLVII. When B is of the above In this followed by reaction said starting

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to processes from commercial obtained by starting from the corresponding aromatic amine prepared, processes. Pharm. starting diazonium group can be azides according when obtained starting chemical al., available, (Campiani corresponding compound XLIV, to acid diazonium φ ct according example, the chlorosulfonyl similar literature (Cornish E.J. acyl carboxylic literature commercially 65). The of the the can be through starting sulfur dioxide of corresponding rearrangement available, compounds not 30 20

(75)

to 24 hours.

time from 4

ದ

room temperature and for

XIVII

900°R

(25)

IIIAX

HO

HNLH

COCH³

зсреше 7

HA - (CH2)"-B- SOSNE,

(92)

III

R90-0-0-0PR

XIIX

H10-A - (CH2)n-B-502CI

1

900°R

XIV

H³C

OH

XIVI

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41

Chem., 1993, 58, 7665).

A starting compound XXIIa,

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XXIIa

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to and general formula XXII with T=CH $_2$, Y-Z=CH $_2$ CH $_2$, starting Ø can be prepared group at the 2example, by prepared þ al., Chem. Pharm. Bull., 1974, 22, 331. A ring can be prepared A compound XXIIa with the hydroxymethyl group at the 3-Urban F.J. et al., J. Heterocyclic Chem., 1991, 29, 431. λ the 4described in literature. Thus, 2-hydroxyacetophenone according example, Augstein J. et al., J. Med. Chem., 1968, 11, 844 example, group at can be obtained can be according to the processes described, for for for Solladie G. et al., Synthesis, 1991, 569. ring position of the dihydrobenzopyran ring compound XXIIa with the hydroxymethyl compound XXIIa with the hydroxymethyl the process described, according to the process described, position of the dihydrobenzopyran position of the dihydrobenzopyran U=oxygen, G=hydrogen and n=1, synthetic processes commercial Okumura K. et according to o t from a

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A starting compound XXIIb,

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Y-Z=CH₂CH₂, G=COOR⁹, U=O, n=1 and with the hydroxymethyl dihydrobenzofuran ring, commercial T=single **ф** suitable following with Ø (Eggler XXII from position of the ester, formula starting literature acid general obtained 4-hydroxybenzoic 2in the described group at Of 4703052). pe

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of general formula position obtained suitable solvent บ์ เ reflux water, tetrahydrofuran, at the 3sodium borohydride, in OL De De 41 0 G=Br subjecting a compound XLVIII to the action solvent can of $Y-Z=CH_2CH_2$, A starting compound XXIIc, i.e. and with the hydroxymethyl group amount dihydrobenzofuran ring, the time from 3 to 24 hours (step 28). Ö temperature between 20°C and catalytic ethanol bond, metal hydride, such as T=single methanol, W ψ. O with as presence the XXII such n=1 of

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XLVIII

XXIIC

A compound XLVIII can be prepared following processes described in literature (Boyle E.A. et al., J. Med. Chem., 1986, 29, 894).

A starting compound XXIId,

IX MTFh B=COOR9 COOH₉ CONH (88) ö (IE) (35)

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XXIId

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T=single bond, with formula XXII G=Br or C1, U=0 general of

through similar transformations of products described in obtained described in literature and n=1, can be to processes Y-Z-CH-CH, according .. e

with compound XXIId Ø literature.

Thereby,

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hydroxymethyl group at the 2- position of the benzofuran process described by Dann O. et al., Liebigs Ann. Chem., hydroxymethy1 obtained, for example, according to the with compound XXIId 1982, 1836. A ring can be

the

28, by reduction of a suitable benzofuran-3-carboxylic according obtained according to the conditions described at (Mustafa A., group at the 3- position of the benzofuran ring Heterocycl. Compd., Weissberger-Taylor Eds., turn & Sons, N.Y., 1974, vol. 29, 114-117). processes described in literature its obtainable in ester,

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step

to

John Wiley

obtained

above for commercial or easily available compounds through similar starting can be described XXII compounds XXIX the processes compounds the one of of starting synthetic methods. the preparation to according

example, according to the synthetic A starting compound IX wherein R7 is hydrogen can process represented in scheme 8 for prepared,

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from

Starting

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hydrogen, described . T 23 process starting compound XVIII, wherein ια literature (JP 03095144, 1991). 40 according obtained

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starting obtained can be compound XXI starting

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concentrated then by 2 hours with potassium 2 hours, Ď, is hydrogen 75°C for of temperature a mixture minutes to copper powder at said reaction mixture R7 ๗ compound XVIII wherein sodium nitrite in at 20 Water time from and in the presence of Ø acid for treatment of with 10.0 sulfuric M first

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corresponding similar primary ď is hydrogen according to R.A.W. of S monoalkylation and XVIII wherein R7 from the described in literature (Johnstone starting the Chem. Soc. C, 1969, 2223). for obtained compounds IX R7 processes compounds wherein group, can be The chemical amines

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according (Huan F.C. prepared can be literature Med. Chem., 1991, 34, 1704). compound XII in described starting processes Ç

C

leukotrienes effects anti-allergic properties and they have prevention bronchial asthma, tendinitis, show Said compounds present invention conditions of the bursitis, psoriasis and related inflammations treatment osteoarthritis, for bioavailability, rhinitis, such mediators are involved. therapy, inflammatory activity of useful in the and the reactions anti-inflammatory in human allergic conjunctivitis, various remarkable antagonistic of oral arthritis, compounds nseq good of them hypersensitivity treatment wherein those therefore Ø which make rheumatoid therefore show

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cardiovascular oedema present invention may myocardic cerebral the oţ anaphylaxis, ischemia, diseases the cardiac oţ cardiac treatment compound of id N Spasm, such the coronary i, system, nseq

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endotoxyc schock.

said the formulated in suitable pharmaceutical of active principle techniques and methods, For the intended therapeutic uses, the compounds and o. capsules, tablets, syrups Handbook, Mack Pub. Co., N.Y. U.S.A. Examples Pharmaceutical containing from 1 to 1000 mg of conventional Remington's formulations include compositions, using in invention are disclosed per unit dose. a Si

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BXAMPLES

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The following examples illustrate the preparation of the compounds of the present invention.

Example 1: 8-[2-(Benzyloxymethyl)chromane-6-carboxami-dol-4-oxo-4H-1-benzopyran-2-carboxylic acid

15 1A Ethyl 4-oxo-4H-1-benzopyran-2-carboxylate

A 2,68 M sodium ethoxide solution in ethanol (21,9 (3.98 ml, 29.4 mmol) in a mixture of dry ethyl ether (20 solution of 2-hydroxystirred under reflux for 3 h. Afterwards it was diluted oxalate added with 1M HCl (25 ml) and extracted with ethyl ether (3x40 ml). The combined ether removed by evaporation under reduced pressure. The obtained residue was dissolved in absolute ethanol (60 ml) and 0.380 ml resulting mixture was left under stirring at 75°C for 1 on the organic phase was washed successively with mixture added. poured diethyl Were The concentrated hydrochloric acid were of water were which was extracted with ethyl mmol) and absolute ethanol (20 ml). solvents ø acetophenone (1.76 ml, 14.7 the was added slowly to h. After this time, 50 ml with ethyl ether (40 ml), and dried Were and ml). The mixture phases

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product æ solvents ethyl obtain and crystallization in title pressure, to solution the the and saturated of dried off under reduced D) 2.660 рх solution, bicarbonate purified thereby obtaining evaporated saturated sodium yield). 1H N.M.R. (300 MHz, CDCl₃) & ppm: 1.41 (t, 3H); 4.43 (q, 2H); 7.08 (s, 1H); 7.42 (t, 1H); 7.59 (d, 1H); 7.71 (t, 1H); 8.16 (dd, 1H).

1B Ethyl 2-chromanecarboxylate

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Was for 4-oxo-4H-1-benzopyran-2sodium saturated redissolved evaporated off under reduced pressure, to obtain 1.57 palladium-on-charcoal and the mixture and temperature acetic acid (20 ml) solvent 09) the filtrate successively with a 5% methanol chloride After dried and the Was carboxylate (2.0 g, 9.17 mmol) in atmosphere. dryness. The residue sodium left under stirring at room pressure off and the title product (84% yield). glacial ethyl ್ mixture was solution and hydrogen filtered washed chloroform (25 ml) and of solution and added with 10% solution. The under evaporated to catalyst was ether bicarbonate

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1H N.M.R. (300 MHz, CDCl₃) & ppm: 1.38 (t, 3H); 2.01-2.29 (sc, 2H); 2.78 (m, 2H); 4.21 (q, 2H); 4.69 (dd, 1H); 6.82 (t, 1H); 6.90 (d, 1H); 7.01 (d, 1H); 7.09 (t, 1H).

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1C 2-Chromanemethanol

A solution of ethyl 2-chromanecarboxylate (1.575 g, 7.68 mmol) in a mixture of tetrahydrofuran (75 ml) and water (2 ml) was added with sodium borohydride (0.686 g,

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r. and the mixture was left mixture was extracted with dichloromethane. The combined organic 48 h. Afterwards acetone was removed by thereby obtaining 0.5 at -10°C and added with the for Subsequently water (100 ml) was added and temperature 1.218 g of the title product (97% yield). stirring at room temperature for dried and the solvent under reduced pressure, room small portions at was cooled ml) stirring mmol) in were mixture evaporation

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¹H N.M.R. (300 MHz, CDCl₃) 6 ppm: 1.87 (m, 1H); 1.94 (m, 1H); 2.76 (m, 1H); 2.90 (m, (dd, 1H); 3.85 (dd, 1H); 4.13 (m, 1H); (broad s, 1H); 7.07 (sc, 2H). 2.18

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1D 2-(Benzyloxymethyl)chromane

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17.8 mmol, previously washed with TOOM atmosphere, with 2-chrodissolved in N,Ndimethylformamide (15 ml) and the mixture was left under of benzyl bromide (2.12 ml, 17.8 mmol) in N,Nadded and the solvent was evaporated off under reduced ether (70 ml), the extracted phases partitioned in 60% sodium hydride dispersion petroleum ether) in dry N,N-dimethylformamide crystals HI) with ethyl ether (3x70 ml). The combined organic tetrabutylammonium iodide were added stirring (10 aqueous one was water some room temperature for 1 h. pressure. The obtained residue was g, 7.43 mmol) temperature for 18 h. Afterwards, of water (70 ml) and ethyl ml) and solvent was phases were separated and the added; under inert (20 mineral oil (0.711 g, suspension of manemethanol (1.218 and the dimethylformamide stirring at dried solution MASS mixture were

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purified column 1.569 gel crude which was 9:1 the title product were recovered (83% yield) silica ether, through a ether:ethyl obtain a chromatography petroleum Ç pressure, with Eluting reduced

¹H N.M.R. (300 MHz, CDCl₃) 5 Ppm: 1.85 (m, 1H); 2.04 (m, 6.79-6.85 2.87 (m, 1H); 3.61 (dd, 1H); 7.00-7.10 (sc, 2H); 7.25-7.36 (sc, 5H) 1H); 4.62 (s, 2H); 2.74 (m, 1H); 4.21 (m, 1H); 2H);

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1E 2-(Benzyloxymethyl)-6-chromanecarbaldehyde

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30 N-methylformanilide (1.14 ml, 9.26 mmol) and the mixture Subsequenly the mixture was diluted with dichloromethane solution (20 acid solution After drying pressure, a residue was obtained which was purified by H. for added very slowly and under inert atmosphere organic phase 9.26 mmol) of minutes. After that 2-(benzyloxymethyl)chromane 65°C for temperature evaporation under gel 0.921 acetate sodium chloride saturated solution. washed successively with a 1M hydrochloric silica Phosphorous oxychloride (0.863 ml, 10:1, title product were recovered (53% yield). 6.18 mmol) was added stirring at separated and the room Eluting with hexane:ethyl acetate, a 15% sodium ๗ through Ω C‡ removing the solvent by stirring flash chromatography ml), added with ml), the phases were left under and

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5H); CDC1₃) 5 ppm: 1.92 (m, 1H); 2.04 (m, 2.89 (m, 2H); 3.70 (dd, 1H); 3.76 (dd, 1H); (m, 1H); 4.68 (s, 2H); 6.98 (d, 1H); 7.32-7.41 (sc, 7.64 (sc, 2H); 9.87 (s, 1H). ¹H N.M.R. (300 MHz,

25

1F 2-(Benzyloxymethyl)-6-chromanecarboxylic acid

2-(benzyloxymethyl)-6-chromane solution of

under

off

evaporated

27

The XAS added at 0°C with Jones reagent, consisting of a mixture (0.326 g, 3.27 mmol), water (0.95 for 18 h. After that, a mixture of isopropyl alcohol (10 ml) and water (50 ml) was added, extracting with ethyl ether (3x30 ml). The organic phase was dried and the solvents to obtain a Q column. Eluting with hexane:ethyl acetate, g of the title compound were obtained (60% residue which was purified by chromatography through in acetone (5 ml) mixture was left under stirring at room temperature m1). acid (0.27 were evaporated off under reduced pressure sulfuric baldehyde (0.921 g, 3.27 mmol) and concentrated trioxide chromium silica gel 0.580

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1H N.M.R. (300 MHz, CDCl₃) 5 ppm: 1.87 (m, 1H); 2.08 (m, 1H); 2.84 (m, 2H); 3.65 (dd, 1H); 3.72 (dd, 1H); 4.29 (m, 1H); 4.62 (s, 2H); 6.88 (d, 1H); 7.32-7.40 (sc, 5H); 7.82 (sc, 2H).

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1G 4-Bromophenyl acetate

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H 100 ml of chloroform was added at 0°C with triethylamine stirring at the solvent 0.145 mol) mixture colourless was evaporated off under reduced pressure, dried and After that the (16.4 ml) solution of 4-bromophenol (25 g, Q S 0.2M HCl solution, (20.1 ml) and acetic anhydride compound temperature for 2 h. title (quantitative yield) the washed with a obtaining

1H 5-Bromo-2-hydroxyacetophenone

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A mixture of 4-bromophenyl acetate (31.3 g, 0.145 mol) and AlCl₃ (47.3 g) was heated at 120°C for 2 h. Afterwards the mixture was left to cool at a temperature of about 50°C and added carefully with a mixture of ice

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ml). to obtain a crude a silica 9:1, thereby to prepare mJ). temperature and extracted with ethyl acetate (4x100 t) solvent recovering 23.7 g of the title compound (76% yield) concentrated hydrochloric acid (15 cooled through with hexane:chloroform, 100°C Was chromatography evaporated off under reduced pressure, and at that dried heated After was ρλ Was solution. organic phase eluting purified mixture g) and homogeneous column, which was resulting (70

S

1H N.M.R. (300 MHz, CDCl₃) & ppm: 2.56 (s, 3H); 6.78 (d, 1H); 7.43 (dd, 1H); 7.72 (d, 1H); 12.10 (s, 1H).

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11 5-Bromo-2-hydroxy-3-nitroacetophenone

with concentrated nitric acid (17.2 ml). The mixture was The precipitated solid was then left light yellow solid 5-bromo-2-hydroxyacetophenone 20.9 g cold mI) under stirring at 75°C for 50 minutes, carbon tetrachloride (90 After drying under vacuum, washing m as temperature. were obtained filtration of 0.110 mol) in solution tetrachloride. at room recovered by title product yield). left

1H N.M.R. (300 MHz, CDCl₃) & ppm: 2.73 (s, 3H); 8.14 (d 1H); 8.31 (d, 1H); 12.92 (s, 1H).

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1J_3-Amino-2-hydroxyacetophenone

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5-bromo-2-hydroxy-3-nitroacetophenone hydrobromide (quantitative point the 9:1, at described methanol:dichloromethane, process the O obtained the from Following in compound was dissolved starting yield). 1H N.M.R. (300 MHz, CD₃0D) & ppm: 2.72 (s, 3H); 7.13 (t, 1H); 7.69 (dd, 1H); 8.08 (dd, 1H).

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53 1K N-(3-Acetvl-2-hydroxyphenyl)-2-(benzyloxymethyl) chromane-6-carboxamide

u)

(5.98 ml) was heated at 75°C for 35 minutes. The oxalyl evaporated off in a nitrogen stream 2-(benzyloxymethyl)-6-chromanecarminimum solution was 3-amino-2-hydroxyacetophenone (0.550 g, 2.37 mmol), ml) and dry methylene chloride (40 ml). The a solution of methylene under reduced pressure. A crude was obtained which was purified by chromatography the title compound stirring at and chloride (40 ml), washed successively with 1M HCl ether:chloroform mixtures of increasing polarity. dissolved in the oxalyl solution, dried with with added at 0°C and under inert atmosphere to This in silica gel column, eluting diluted 0.732 g of left under acid (0.700 g, 2.35 mmol) chloride. Was temperature for 18 h, then saturated off and the resulting residue of dry methylene 40% chloroform proportion, Was evaporated were eluted (72% yield). suspension of chloride excess was mixture chloride Kas pyridine (7 resulting Ø boxylic through solvent amount sodium

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1H N.M.R. (300 MHz, CDCl₃) & PPm: 1.92 (m, 1H); 2.14 (m, 1H); 2.70 (s, 3H); 2.93 (m, 2H); 3.70 (dd, 1H); 3.78 (dd, 1H); 4.62 (s, 2H); 7.00 (m, 2H); 7.30-7.42 (sc, 5H); 7.51 (d, 1H); 7.70 (sc, 2H); 8.09 (s, 1H); 8.80 (d, 1H); 13.01 (s, 1H).

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1L Ethyl 8-[2-(benzyloxymethyl)chromane-6-carboxamidol-4-oxo-4H-1-benzopyran-2-carboxylate

Following the process described at point A, starting from N-(3-acetyl-2-hydroxyphenyl)-2-(benzyloxy-methyl)chromane-6-carboxamide and diethyl oxalate, the

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54 title compound was prepared, which was purified by warm crystallization in ethyl acetate (66 % yield).

1H N.M.R. (300 MHz, CDCl₃) 6 ppm: 1.47 (t, 3H); 1.90 (m, 1H); 2.11 (m, 1H); 2.89 (m, 2H); 3.67 (dd, 1H); 3.75 (dd, 1H); 4.32 (m, 1H); 4.49 (q, 2H); 4.65 (s, 2H); 6.95 (d, 1H); 7.15 (s, 1H); 7.30-7.40 (sc, 5H); 7.47 (t, 1H); 7.70 (dd, 1H); 7.78 (d, 1H); 7.88 (dd, 1H); 8.74 (s, 1H); 8.93 (dd, 1H).

L/)

1M 8-[2-(Benzyloxymethyl)chromane-6-carboxamidol-4-oxo-4H-1-benzopyran-2-carboxylic acid

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ethyl 8-[2-(benzyloxymethyl)chro- $\verb|mane-6-carboxamido]-4-oxo-4 \textit{H-}1-benzopyran-2-carboxylate|$ evaporated to dryness suspended in water adding and tetrahydrofuran (15 ml) was added with 0.510 ml 1M NaOH solution, stirring at room temperature for on phosphorous pentoxyde under vacuum, methano1 solid was recovered by filtration, washed with g of the title compound as Hď which decomposes above 283°C (97% yield). oţ acid a mixture acid to slightly that the mixture was residue was g, 0.47 mmol) in of suspension obtaining 0.221 the resulting hydrochloric and dried h. After (0.240)

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1H N.M.R. (300 MHz, CD₃OD/CDCl₃ mixtures) 6 ppm: 1.82
(m, 1H); 2.12 (m, 1H); 2.85 (m, 2H); 3.62 (dd, 1H); 3.67
(dd, 1H); 4.23 (m, 1H); 4.57 (s, 2H); 6.85 (d, 1H); 7.01
(s, 1H); 7.20-7.30 (sc, 5H); 7.38 (t, 1H); 7.69 (m, 2H);
7.83 (dd, 1H); 8.48 (dd, 1H).

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Example 2: N-f4-Oxo-2-(1H-5-tetrazoly1)-4H-1-benzopyran-8-v11-2-(benzyloxymethy1)chromane-6-carboxamide

30 2A Ethyl 6-bromo-8-nitro-4-oxo-4H-1-benzopyran-2-carbo-xylate

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5-bromo-2-hydroxy-3-nitroacetophenone (point was prepared, tetrahydro-Following the process described in example 1 i. compound purified by crystallization furan:ethanol mixtures (77% yield). title oxalate, the from starting diethyl which was and

1H N.M.R. (300 MHz, CDCl₃) & ppm: 1.45 (t, 3H); 4.49 (q, 2H); 7.21 (s, 1H); 8.48 (d, 1H); 8.58 (d, 1H).

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2B Ethyl 8-nitro-4-oxo-4R-benzopyran-2-carboxylate

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10% The 6-bromo-8-nitro-4-oxo-4H-1m] time the at 145°C mixture was left to cool and the catalyst was removed by the through hexane:chloroform, formic acid (7.90 and filtration, washing it with N,N-dimethylformamide. recovered mmol), obtained residue was purified by chromatography evaporated to dryness and N, N-dimethylformamide (42 ml) was stirred this 14.6 After of the title product were with þ inert atmosphere. palladium-on-charcoal (0.541 g), benzopyran-2-carboxylate (5.0 Eluting ethyl filtrate was column. of mixture under 85:15, 2.109 g gel 5.75 h resulting silica yield).

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1H N.M.R. (300 MHz, CDCl₃) & ppm: 1.46 (t, 3H); 4.50 (q, 2H); 7.21 (s, 1H); 7.61 (t, 1H); 8.41 (dd, 1H); 8.49 (dd, 1H).

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2C 8-Nitro-4-oxo-4H-1-benzopyran-2-carboxamide

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suspended in concentrated ml). After ethanol temperature 8-nitro-4-oxo-4H-benzopyran-2 H and minutes in anhydrous dryness ml) and anhydrous tetrahydrofuran (50 LOOM 30 hydrochloric acid (20 ml) stirring at 40 for evaporated g, 8.02 mmol) bubbled resulting solid residue was ammonia was the mixture was ethy1 carboxylate (2.109 O. Gas solution that

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repeatedly phosphorous diluted with water, product Washed no title vacuum filtration, the 4. O Then the mixture was under 5 obtain 1.515 recovered by dried and pentoxyde, to Mass 'n. yield). solid

1H N.M.R. (300 MHz, DMSO) 5 ppm: 7.01 (s, 1H); 7.75 (t, 1H); 8.01 (broad s, 1H); 8.37 (broad s, 1H); 8.43 (dd, 1H); 8.61 (dd, 1H).

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2D 8-Nitro-4-oxo-4H-1-benzopyran-2-carbonitrile

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stirring at room temperature N, N-dimethylformamide (10 ml) was added and the mixture a residue was obtained solution of 8-nitro-4-oxoä ethy1 silica 1.094 g After this time, the reaction mixture was poured onto temperature for 18 mmol) (40 ml) removing added extracted with ι¢ gel column. Eluting with hexane:chloroform, 7:3, 6.47 purified by chromatography through title product were recovered (78% yield) to dry N,N-dimethylformamide מ mI) (1.515)drying (2.86)and room reduced pressure, rø 4H-1-benzopyran-2-carboxamide Phosphorous oxychloride m1) ml). After stirring at that under (100 After the mixture was left mixture (4×40 minutes. under solvents under ပ. ၀ slowly at which was ice-water left acetate

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¹H N.M.R. (300 MHz, DMSO) 6 ppm: 7.01 (s, 1H); 7.70 (t, 1H); 8.38 (dd, 1H); 8.56 (dd, 1H).

2E_8-Nitro-4-oxo-2-(5-1H-tetrazoly1)-4H-1-benzopyran

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(1.638)8-nitro-4-oxo-4H-1-benzopyran-2mixture left mmol), sodium azide MAS the D) (1.349)that N, N-dimethylformamide (50 ml) After ammonium chloride 1.25 h. 5.06 Dì of at 100°C for carbonitrile (1.094 mixture mmol), dry 25.3 and

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solution (50 ml) recovering the formed time and m1) organic evaporated off under เต mI) (12 for 2.5 h. After this resulting solid the onto The acid diluted with water (50 O£ acetate (4x30 ml). D) poured hydrochloric 0.896 and phase was dried and the solvent was reduced pressure, thereby obtaining The temperature stirring at room temperature filtration. suspended in concentrated mixture was ethy1 product (69% yield). hydrochloric acid TOOM þХ with precipitate at extracted acid cooled

S

1H N.M.R. (300 MHz, DMSO) & ppm: 7.21 (s, 1H); 7.73 (t, 1H); 8.41 (dd, 1H); 8.55 (c3, 1H).

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2F 8-Amino-4-oxo-2-(5-1H-tetrazolyl)-4H-1-benzopyran

Following the process described in example 1 (point tetrazolyl)-4H-1-benzopyran (0.896 g, 3.46 mmol) with 5% 8-nitro-4-oxo-2-(5-1Hmethanol its corresponding hydrochloride (quantitacompound (91 mg) in a mixture of and the title ml) B), by hydrogenating for 4 h chloroform (20 m1), acid (2 Palladium-on-charcoal hydrochloric a S ml), prepared

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1H N.M.R. (300 MHz, CD₃OD) & ppm: 7.25 (s, 1H); 7.62 (t, 1H); 7.94 (d, 1H); 8.14 (d, 1H). 2G N-[4-0xo-2-(1H-5-tetrazolv1)-4H-1-benzopyran-8-v1]-2-(benzyloxymethyl)chromane-6-carboxamide

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Following the process described in example 1 (point K), starting from 2-(benzyloxymethyl)-6-chromanecarboxylic acid and 8-amino-4-oxo-2-(5-1*H*-tetrazolyl)-4*H*-1-benzopyran, the title compound was prepared as a white solid with melting point 214-216°C, which was purified by crystallization in methanol (57% yield).

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Example 3: 8-[2-(3-Phenylpropyl)chromane-6-carboxamidols, 1H). 1H); 1H); 2H); 6.89 (d, 7.87 (dd, 1H); 8.59 (dd, 1H); 8.80 (broad 3.62 (dd, (300 MHz, CD₃OD/CDCl₃ mixtures) 8 7.20-7.34 (sc, 5H); 7.44 (t, 1H); 4-oxo-4H-1-benzopyran-2-carboxylic acid 2H); 4.58 (s, 2.85 (m, 1H); 4.23 (m, 1H); 2.12 (m, 1H); 1H); 1H N.M.R. 1H);

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3A 2-Chromanemethyl trifluoromethanesulfonate

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with successively with IN HCl, 5% NaHCO3 aqueous phase was extracted drying and removing 6.53 mmol) ပ် • É mmol) and pyridine (1.05 ml) in dry dichloromethane 18 h at added Ď g of the title compound (82% yield) then it was diluted with dichloromethane (20 ml), The combined silica gel column, solvents, a residue was obtained which was mixture, (0.765)E, atmosphere was stirring for anhydride (1.10 2-chromanemethanol acetate 9:1 solution. After dichloromethane (3x20 ml). left under O°C and under inert chromatography through a and the trifluoromethanesulfonic hexane:ethyl a NaCl saturated of (300 MHz, the mixture was with water (25 ml) phases were washed mixture 1.381 1H N.M.R. obtaining rd at with with ml) and and

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1H N.M.R. (300 MHz, CDCl₃) 6 ppm: 1.90 (m, 1H); 2.05
1H); 2.82 (m, 1H); 2.93 (m, 1H); 4.33 (m, 1H); 4.64
2H); 6.86 (m, 2H); 7.07 (m, 2H).

3B 2-(3-Phenylpropyl)chromane

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ml, 12.6 mmol) in mmol) in atmosphere magnesium (0.304 g, 12.6 ml) with a iodine (1.72)drop and under inert The 2-bromoethylbenzene m1). (12 tetrahydrofuran (5 suspension of tetrahydrofuran added drop by solution of dry

ROOM (163 mg, 0.79 mmol) in tetrahydrofuran (2 ပ • • 0 2-chromanemethyl ammonium After this time, the mixture was poured slowly onto a chloride saturated aqueous solution (20 ml). The phases separated and the aqueous phase was extracted with dichloromethane (4x25 ml). The combined organic extracts crude which was purified of solvent was evaporated off under מ solution mmol) tetrahydrofuran (5 ml) were added successively at and the mixture was left under stirring at 0°C for 0.990 gel column, an 4.67 left 9:1, to recover and ĸ מׁ that Kas Kas m]) 0 1 by chromatography through a silica trifluoromethanesulfonate (1.381 dichloromethane (25 addition, After ಗ solution the title product (85% yield) with hexane:dichloromethane, obtain ц . 2.5 bromide to the reduced pressure, for and $CuBr.(CH_3)_2S$ of the temperature dried mixture during Were

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1H N.M.R. (300 MHz, CDCl3) 6 Ppm: 1.60-2.00 (sc, 6H);
2.67 (t, 2H); 2.70-2.88 (sc, 2H); 3.98 (m, 1H); 6.80 (m, 2H); 7.03 (m, 2H); 7.17-7.28 (sc, 5H).

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3C 2-(3-Phenylpropyl)-6-chromanecarbaldehyde

Following the process described in example 1 (point E), starting from 2-(3-phenylpropyl)chromane, the title compound was prepared (66% yield).

1H N.M.R. (300 MHz, CDCl₃) 5 ppm: 1.60-2.00 (sc, 6H);
2.68 (t, 2H); 2.82 (m, 2H); 4.08 (m, 1H); 6.88 (d, 1H);
7.18 (m, 3H); 7.26 (m, 2H); 7.60 (m, 2H); 9.81 (s, 1H).
3D 2-(3-Phenylpropyl)-6-chromanecarboxylic acid

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Following the process described in example 1 (point F), starting from 2-(3-phenylpropyl)-6-chromanecarbaldehyde, the title compound was prepared (66% yield).

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60 2.73 (t, 2H); 2.88 (m, 2H); 4.12 (m, 1H); 6.87 (d, 1H); 7.20 (m, 3H); 7.31 (m, 2H); 7.88 (m, 2H).

3E N-(3-Acetyl-2-hydroxyphenyl)-2-(3-phenylpropyl)

chromane-6-carboxamide

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Following the process described in example 1 (point K), starting from 2-(3-phenylpropyl)-6-chromanecarboxylic acid and 3-amino-2-hydroxyacetophenone, the title compound was prepared (45% yield).

6H); 1H); 7.51 (d, 1.65-2.10 (sc, 4.10 (m, 5H); (sc, 2.88 (m, 2H); 1H); 6.99 (t, 1H); 7.20-7.35 2H); 8.58 (broad s, : ш**dd** 9 1H N.M.R. (300 MHz, CDC13) 2.73 (m, 2H); 7.68 (m, 13.01 (s, 1H). 2.70 (s, 3H); 6.89 (d, 1H); 1H);

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3F Ethyl 8-[2-(3-phenylpropyl)chromane-6-carboxamidol-4-oxo-4H-1-benzopyran-2-carboxylate

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Following the process described in example 1 (point A), starting from N-(3-acetyl-2-hydroxyphenyl)-2-(3-phenylpropyl)chromane-6-carboxamide and diethyl oxalate, the title compound was prepared, which was purified by chromatography through a silica gel column, eluting with chloroform (47% yield).

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1H N.M.R. (300 MHz, CDCl₃) & ppm: 1.48 (t, 3H); 1.65-2.10 (sc, 6H); 2.71 (t, 2H); 2.89 (m, 2H); 4.10 (m, 1H); 4.50 (q, 2H); 6.90 (d, 1H); 7.17 (s, 1H); 7.20-7.35 (sc, 5H); 7.48 (t, 1H); 7.70 (dd, 1H); 7.79 (d, 1H); 7.88 (dd, 1H); 8.74 (s, 1H); 8.93 (dd, 1H).

3H 8-[2-(3-Phenylpropyl)chromane-6-carboxamidol-4-oxo-4H-1-benzopyran-2-carboxylic acid

Following the process described in example 1 (point M), starting from ethyl 8-[2-(3-phenylpropyl)chromane-6-

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carboxamido]-4-oxo-4H-1-benzopyran-2-carboxylate, the title compound was prepared as a white solid with melting point 325-326°C (80% yield).

1H N.M.R. (300 MHz, CD₃OD/CDCl₃ mixtures) 6 ppm: 1.65-2.10 (sc, 6H); 2.73 (t, 2H); 2.90 (m, 2H); 4.10 (m, 1H); 6.89 (d, 1H); 7.09 (s, 1H); 7.20-7.35 (sc, 5H); 7.47 (t, 1H); 7.77 (m, 2H); 7.92 (dd, 1H); 8.56 (dd, 1H).

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Example 4: N-[4-0xo-2-(1H-5-tetrazoly1)-4H-1-benzopyran-8-v11-2-(3-phenylpropy1)chromane-6-carboxamide

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Following the process described in example 2 (point K), starting from 2-(3-phenylpropyl)-6-chromanecarboxylic acid and 8-amino-4-oxo-2-(5-1H-tetrazolyl)-4H-1-benzopyran, the title compound was prepared as a white solid which decomposes at temperatures higher than 370°C and which was purified by crystallization in methanol (65% yield).

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1H N.M.R. (300 MHz, CD₃OD/CDCl₃ mixtures) 5 ppm: 1.65-2.10 (sc, 6H); 2.71 (t, 2H); 2.90 (m, 2H); 4.11 (m, 1H); 6.89 (d, 1H); 7.15-7.35 (sc, 6H); 7.49 (t, 1H); 7.79 (m, 2H); 7.95 (d, 1H); 8.60 (d, 1H).

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Example 5: 8-[2-(Benzyloxymethyl)benzofuran-5-carboxami-dol-4-oxo-4H-1-benzopyran-2-carboxylic acid

5A (4-Bromo-2-formyl)phenyloxyacetonitrile

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mmol), potassium carbonate (3.78 g, 26.8 mmol) and N,Ndimethylformamide (70 ml) was added with a solution of (10 ml), then with a catalytic mixture was 5 at 80°C for 1.5 h, then was ethyl potassium iodide. The resulting of 5-bromosalicylaldehyde 24.8 and extracted with (1.87)N, N-dimethylformamide (50 ml) stirring chloroacetonitrile A mixture Water left under amount of with

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(4x75 ml). The combined organic phases were dried and the solvents were removed under reduced pressure, to obtain 5.126 g of the title compound (98% yield).

1H N.M.R. (300 MHz, CDCl₃) 6 ppm: 4.93 (s, 2H); 7.01 1H); 7.73 (dd, 1H); 8.00 (d, 1H).

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(g)

58 5-Bromo-2-benzofurancarboxylic acid

after that was diluted with water (75 ml) and acidified with 1M hydrochloric acid. The volatiles were evaporated reduced pressure and the resulting aqueous (4-bromo-2-formyl)phenyloxy-acetonipotassium hydroxide (6.0 ethyl acetate (4x100 ml). a yellow solid with melting point the pressure, and Was dried ethanol (250 ml) off under reduced combined organic phases were mmol), extracted with 21.3 O.f (98% yield). compound as mixture ğ absolute trile (5.11 residue was evaporated under title and

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5C Ethyl 5-bromo-2-benzofurancarboxylate

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acid Was the residue was neutralized with off under reduced solid dried ml) and 2 h. After 5-bromo-2-benzofurancarboxylic a white (150 ml) solution and Was reduced acid (15 ethanol S mixture mixture was refluxed under stirring for of the title compound off under evaporated with melting point 58-60°C (93% yield) in absolute sulfuric m1). The saturated evaporated pressure and the resulting the volatiles were concentrated ether (4x100 bicarbonate mmol) solution of Ø the solvent was 5.19 20.8 with Ó to obtain sodium added

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1H N.M.R. (300 MHz, CDCl₃) & ppm: 1.34 (t, 3H); 4.35 (q, 2H); 7.39 (m, 3H); 7.71 (d, 1H).

5D (5-Bromo-2-benzofuranyl)methanol

S

ethyl 5-bromo-2-benzofurancarboxylate added of stirring for 18 h drops of and chromatography the title product solvent under reduced pressure, drops drying concentrated HCl. The volatiles were evaporated off melting point Water g, 8.19 mmol) in tetrahydrofuran (75 ml) was Some eluting with ethyl ether (3x75 ml). After some With purified by sodium borohydride (1.24 g) and mixture was refluxed under with resulting residue was diluted a white solid with g of added gel column, 60:40. 1.19 obtained which was Kan the that, solution of silica ether:chloroform, 103°C (64% yield). recovered as evaporating off with water. The through a extracted crude was (2.20)

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1H N.M.R. (300 MHz, CDCl₃) 6 ppm: 2.10 (broad s, 1H); 4.76 (s, 2H); 6.60 (s, 1H); 7.33 (m, 2H); 7.66 (s, 1H).

20 5E 2-(Hydroxymethyl)benzofuran-5-carbonitrile

and (1.19)mmol) under organic 0 £ £ reduced pressure. The resulting crude was purified of increasing title product ml) solvents were evaporated 5.25 5-bromo-2-benzofuranylmethanol left 200°C for 3.5 h, then was poured g) in water (80 column, m1). The cyanide (0.470 g, Was chromatography through a silica gel acetate mixtures thereby obtaining 0.671 g of ml) acetate (3x75 (15 ethylenediamine (6 N-methylpyrrolidinone (I) the copper ethy1 and n-hexane:ethyl solution of dried extracted with mmol), Ω π solution of polarity, stirring phase under

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a yellow solid with melting point 113-114°C (74% yield).

¹H N.M.R. (300 MHz, CDCl₃) 6 ppm: 4.82 (s, 2H); 6.74 (s, 1H); 7.54 (m, 2H); 7.87 (s, 1H).

5F. 2-(Benzyloxymethyl)benzofuran-5-carbonitrile

3.89 oil was washed by decantation with 410 and anhydrous nmol) in benzene (10 ml) stirring at room temperature for at room temperature acetate (4x50 ml). The organic phase was dried ပ.၀ (hydroxymethyl)benzofuran-5-carbonitrile (0.671 mg, Ö extracted which mixtures (0.825 ml) gel dispersion of potassium hydride (0.990 added at solution crude silica tetrabutylammonium resuspended acetate then added with water (50 ml) and with benzyl bromide æ ιΩ through obtain This suspension with stirring n-hexane:ethyl Was purified by chromatography 40 atmosphere anhydrous hexane, then mixture was left under removed, of in 20% mineral m1). amount 15 min, then with under inert solvent (25 catalytic penzene eluting mmo1) ethyl S 10 75 20

4.55 7.79 of מ 2H); 2H); recovering 1.087 compound as a yellowish oil (82% yield). 4.54 (s, 7.45 (s, (300 MHz, CDCl₃) 8 ppm: 5H); polarity, thereby 7.28 (m, 1H); increasing 99.9 1H N.M.R. 2H); 1H).

5G 2-(Benzyloxymethyl)benzofuran-5-carboxylic acid

2-(benzyloxymethyl)benzofuran-5-car with (TE The the for 3 h. After that the mixture was acidified and was extracted with ethyl acetate (4x100 ml). ethanol refluxed evaporated off mmol) in and (55 ml) 4.13 volatiles were 35% NaOH o. מ (1.087)solution added with bonitrile HCl, the

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solid with melting point 129-132°C phase was dried and the solvent was evaporated off under of Ç1 1.165 obtain to as a white (quantitative yield). pressure, compound reduced

1H N.M.R. (300 MHz, CDCl3) & ppm: 4.67 (s, 4H); 6.81 (s, 8.41 8.12 (d, 1H); 7.56 (d, 1H); 7.40 (m, 5H);

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N-(3-Acetyl-2-hydroxyphenyl)-2-(benzyloxymethyl)benzofuran-5-carboxamide 云

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with the Following the process described in example 1 (point 2-(benzyloxymethyl)benzofuran-5-4.60 (s, chromatography through a silica gel column (98% yield). 7.41 acid and 3-amino-2-hydroxyacetophenone, solid 3H); 5H); 8.10 (d, 1H); compound was prepared as a yellowish 2.58 (s, 7.34 (m, Was which ¹H N.M.R. (300 MHz, CDCl₃) 5 ppm: 6.91 (t, 1H); 7.82 (d, 1H); 92-94°C, from 1H); 4H); 6.74 (d, 1H); 8.73 (d, 1H). point starting 7.51 (d, carboxylic 1H);

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8-[2-(Benzyloxymethyl)benzofuran-5-carboxamidol-4oxo-4*H*-1-benzopyran-2-carboxylic acid 20

prepared the ethyl 8-[2-(benzyloxymethyl)benzofuran-5-carboxasubsequently hydrolysed according to the (point from N-(3-acetyl-2-hydroxyphenyl)-2-(benyield example 1 Nas (point M) to with melting mido]-4-oxo-4H-1-benzopyran-2-carboxylate and described in zyloxymethyl)benzofuran-5-carboxamide white solid example 1 Following the process 218°C (65% global yield). described in ಗ compound as starting Kas

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2H); 4.61 (s, 5 ppm: ¹H N.M.R. (300 MHz, DMSO)

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ָׁם (מַ 8.09 7.57 5H); 1H); (H) (g' 7.38 8.02 (s, 1H); 7.93 (d, 1H); 7.11 1H); 1H); 1H). (ď, (s, (8) 6.97 7.76 8.38 2H); 1H);

8-(2-Benzyloxymethyl-2.3-dihydrobenzofuran-5carboxamido -4-oxo-4H-1-benzopyran-2-carboxylic acid Example 6:

6A Ethyl 4-allyloxybenzoate

S

60.2 the mixture was refluxed for 18 h. After reduced pressure, thereby mmo1) (7.22)4-hydroxybenzoate (10.0 g, off allyl bromide only carbonate was filtered , הם containing (8.32)acetone (50 ml) was added with carbonate under crude ethyl evaporated ៧ potassium O.F compound (99% yield). o T O ס potassium 66.2 mmol) and obtaining 12.3 Was mmol) and that

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6.03 (300 MHz, CDC13) 6 ppm: 1.36 (t, 3H); 4.32 (q, 5.40 (dd, 1H); 5.28 (dd, 1H); (m, 1H); 6.90 (d, 2H); 7.98 (d, 2H). 2H); 4.54 (d, 2H); 1H N.M.R.

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6B Ethyl 3-allyl-4-hydroxybenzoate

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A mixture of ethyl 4-allyloxybenzoate (10.0 g, 48.5 ethy1 869) punodwoo mmol) and N,N-dimethylaniline (20 ml) was left diluted with acetate, ø with 1M HC1. After WAS which was purified by chromatography through crude g of the title eluting with n-hexane:ethyl and evaporating off the solvent, a then 200°C for 48 h, and washed recovering 6.85 (150 ml) column, stirring at thereby acetate gel

(ď, 68.9 3.45 1H); 3H); (300 MHz, CDCl₃) & ppm: 1.37 (t, 6.02 (m, 2H); 7.83 (s, 5.14 (d, 2H); (ď) 1H N.M.R. 2H); 4.35

2-hydroxymethyl-2.3-dihydrobenzofuran-5-carbo-Ethyl 얾

1H).

(dd, 1H);

1H); 7.81

67

Jate

acid (11.40 g, 66.1 mmol) and the ethyl acetate and washed with a 1M NaOH solution. After 3-ally1-4-hydroxybenzoate (6.74 Afterwards, crude was obtained silica 90:10, the solvent was evaporated, the crude was redissolved added to recover 5.95 g of the title compound (82% yield). was purified by chromatography through a with n-hexane:ethyl acetate, ml) was stirring for 4 h. solvent, a 32.7 mmol) in chloroform (105 mixture was refluxed under ethy1 drying and removing the meta-chloroperbenzoic gel column, eluting solution of

S

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1H N.M.R. (300 MHz, CDCl₃) 5 ppm: 1.35 (t, 3H); 3.02 (dd, 1H); 3.20 (dd, 1H); 3.74 (dd, 1H); 3.84 (dd, 1H); 4.29 (q, 2H); 4.95 (m, 1H); 6.69 (d, 1H); 7.78 (s, 1H); 7.79 (d, 1H).

6D Ethyl 2-benzyloxymethyl-2.3-dihydrobenzofuran-2-car-boxylate

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Following the process described in example 1 (point D), starting from ethyl 2-hydroxymethyl-2,3-dihydroben-zofuran-5-carboxylate and benzyl bromide, the title compound was prepared, which was purified by chromatography through a silica gel column, eluting with nhexane:ethyl acetate, 95:5 (65% yield).

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1H N.M.R. (300 MHz, CDCl₃) & ppm: 1.32 (t, 3H); 2.93
(dd, 1H); 3.13 (dd, 1H); 3.55 (dd, 1H); 3.59 (dd, 1H);
4.27 (q, 2H); 4.51 (dd, 2H); 4.94 (m, 1H); 6.75 (d, 1H);
7.19-7.27 (sc, 5H); 7.78 (s, 1H); 7.85 (dd, 1H).

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6E 2-Benzyloxymethyl-2.3-dihydrobenzofuran-2-carboxylic acid

A solution of ethyl 2-benzyloxymethyl-2,3-dihydro-benzofuran-2-carboxylate (1.62 g, 5.47 mmol) in methanol

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organic under 1M HCI evaporated off under m1) crystallization refluxed the after that was neutralized with resulting crude was suspended in water (20 The X reduced of ml). o t Ċι. Kas solution under 1.436 acetate (4x25 Was mixture ρλ off phase was dried and the solvent purified obtain ៧ methanol was evaporated ml). The with to ethyl which was added pressure, 3 h, (54.7)extracted with K an hydroxide compound, reduced

S

2H); 7.90 (dd, (dd, 1H); 7.22-7.33 (sc, 5H); 4.60 3.02 3.68 (dd, 1H); CDCl₃) & ppm: (d, 1H); 1H); ¹H N.M.R. (300 MHz, 3.65 (dd, 6.82 1H). (m, 1H); 7.94 (d, (dd, 1H); 1H);

methanol (97% yield).

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6F N-(3-Acetyl-2-hydroxyphenyl)-2-benzyloxymethyl-2.3-dihydrobenzofuran-5-carboxamide

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3,06 1H); 1H); (point 2-benzyloxymethyl-2,3-dihydrobenzofuran-2-carboxylic acid and 3-amino-2-hydroxyacetophenone, solid bγ (74% yield). 3H); (dd, purified 6.85 (t, yellowish described in example 1 1H); 3.70 (s) 1H) 7.72 (d, through a silica gel column 5.06 (m, 1H); 6.86 (d, 1H); (s, 1H); 8.74 (d, 1H), 12.96 (s, 2.64 1H); and ๗ compound was prepared as : mdd (ਰੂਰ, 103-105°C 5H); 7.46 (d, 1H); 3.66 CDCl3) 8 Following the process 1H); point MHZ, (dd, from (300 3.31 chromatography 2H); (sc, melting starting title 1H); (dđ , 7.26-7.34 1H); 8.53 N.M.R.

6G Ethyl 8-(2-benzyloxymethyl-2,3-dihydrobenzofuran-5-carboxamido)-4-oxo-4H-1-benzopyran-2-carboxylate

(point

Following the process described in example 1

N-(3-acety1-2-hydroxypheny1)-2-ben-

from

starting

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and ងន and purified diethyl oxalate, the title compound was prepared zyloxymethyl-2,3-dihydrobenzofuran-5-carboxamide solid with melting point 166-168°C by crystallization in ethanol (73% yield). yellow

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1H); 3.12 1H); 7.15 (s, 1H); 7.30-7.38 (sc, 5H); 7.47 (t, 1H); 7.79 (d, 7.87 (s, 1H); 7.88 (d, 1H); 8.73 (s, 1H); 8.92 (d, (dd, 1H); 3.36 (dd, 1H); 3.70 (dd, 1H); 3.73 (dd, 4.50 (q, 2H); 4.63 (dd, 2H); 5.11 (m, 1H); 6.91 (d, 3H); ¹H N.M.R. (300 MHz, CDCl₃) 8 ppm: 1.47 (t, 1H);

6H 8-(2-Benzyloxymethyl-2.3-dihydrobenzofuran-5-carboxamido)-4-oxo-4H-1-benzopyran-2-carboxylic acid

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3.12 Following the process described in example 1 (point 1H); 8-(2-benzyloxymethyl-2,3-7.30-7.38 (sc, 5H); 7.49 (t, 1H); 7.82 (d, 1H); 7.85 (s, dihydrobenzofuran-5-carboxamido)-4-oxo-4*H*-1-benzopyranyellow solid with melting point 184-188°C (60% yield). ¹H N.M.R. (300 MHz, CD₃OD/CDCl₃ mixtures) 6 ppm: 4.63 (s, 2H); 5.11 (m, 1H); 6.91 (d, 1H); 7.10 (s, 3.36 (dd, 1H); 3.70 (dd, 1H); 3.73 (dd, prepared 2-carboxylate, the title compound was 7.90 (dd, 1H); 8.73 (dd, 1H). ethyl from starting (dd, 1H); 1H);

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Example 7: N-[4-0xo-2-(1H-5-tetrazoly])-4H-1-benzopyran-8-yll-2-benzyloxymethyl-2.3-dihydrobenzofuran-5-carboxa-

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7A N-[4-0xo-2-carbamov1-4H-1-benzopyran-8-v11-2-benzv1oxymethyl-2,3-dihydrobenzofuran-5-carboxamide

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ethyl 8-(2-benzyloxymethyl-2,3dihydrobenzofuran-5-carboxamido)-4-oxo-4*H*-1-benzopyran-(25 2-carboxylate (528 mg, 1.06 mmol) in methanol tetrahydrofuran (25 of solution m and

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with concentrated HCl (0.5 ml). The mixture was refluxed resulting under vacuum on phosphorous pentoxyde, thereby solvents were solid was (quantitative dryness repeatedly with and 40 suspended in water and the insoluble The TE evaporation compound (12 reduced pressure. the tetrahydrofuran:methanol 1:1 mixture Was then filtration, washed title residue After 1.5 h, of the minutes. solid under for ĎE. stirring 30 off 527 resulting ρŽ for evaporated recovered obtaining and dried

M

1H); 1H); ند 1H); 5.12 (m, 1H); \ \ \ \ \ 7.53 8.32 (300 MHz, DMSO) 6 ppm: 3.08 (dd, 5H); 1H); 2H); (sc) ຜ 8.24 (broad (s, 1H); 6.92 (d, 1H); 7.28-7.38 3.70 (m, 2H); 4.57 (s, 7.83-7.89 (sc, 4H); (dd, 1H); N.M.R.

yield).

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N-[4-0xo-2-cyano-4H-1-benzopyran-8-yll-2-benzyloxymethyl-2.3-dihydrobenzofuran-5-carboxamide

8.65 (broad s, 1H).

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(point Q. starting from N-[4-oxo-2-carbamoy]-4H-1-benzopyrancolumn, 8-yl]-2-benzyloxymethyl-2,3-dihydrobenzofuran-5-carboxamixtures ~ gel example which silica ether:chloroform prepared, described in ๗ chromatography through increasing polarity (56% yield). MAS Following the process compound with petroleum title the rified by eluting) (D

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3,35 S 8.30 7.50 1H); 1H); 5H); 5.10 (đđ, 7.77 (s, 1H); 7.88 (dd, 6.92 (d, 1H); 7.28-7.35 (sc, 2H); 3.12 (300 MHz, CDCl₃) & ppm: (dd, 4.64 2H); É) 7.73 (d, 1H); 8.83 (d, 1H). 3.71 (s, 1H); 18); 1H N.M.R. 1H); N-[4-0xo-2-(1R-5-tetrazolyl)-4R-1-benzopyran-8-yl]-2-

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gas

ml), ammonia

anhydrous

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benzyloxymethyl-2.3-dihydrobenzofuran-5-carboxamide

dry acid room N, N-dimethylformamide (10 ml) was left under stirring at solution (10 ml), recovering by filtration the formed of N-[4-oxo-2-cyano-4H-1-benzopyran-8yl]-2-benzyloxymethyl-2,3-dihydrobenzofuran-5-carboxamimmol) and 100°C for 1.25 h. After that the mixture, cooled at de (300 mg, 0.66 mmol), sodium azide (129 mg, poured onto a 1M hydrochloric the crystallization compound as a white solid with melting point methanol:dichloromethane mixtures (68% yield). thereby obtaining 111 mg of chloride (107 mg, 1.99 рХ purified temperature, was mmol), ammonium mixture Was precipitate,

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1H N.M.R. (300 MHz, DMSO) 6 ppm: 3.09 (dd, 1H); 3.37
(dd, 1H); 3.70 (m, 2H); 4.58 (s, 2H); 5.13 (m, 1H); 6.94
(d, 1H); 7.14 (s, 1H); 7.28-7.35 (sc, 5H); 7.57 (t, 1H);
7.87-7.95 (m, 3H); 8.25 (dd, 1H); 10.00 (s, 1H).

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Example 8: 8-[2-(3-Phenylpropyl)-2.3-dihydrobenzofuran-5-carboxamidol-4-oxo-4*H*-1-benzopyran-2-carboxylic acid
8A Ethyl 2-trifluoromethanesulfonyloxymethyl-2.3-dihy-drobenzofuran-5-carboxylate

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Following the process described in example 3 (point A), starting from ethyl 2-hydroxymethyl-2,3-dihydroben-zofuran-5-carboxylate, the title compound was prepared (88% yield).

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1H N.M.R. (300 MHz, CDCl₃) 6 ppm: 1.38 (t, 3H); 3.07
(dd, 1H); 3.44 (dd, 1H); 4.34 (q, 2H); 4.60 (dd, 1H);
4.67 (dd, 1H); 5.17 (m, 1H); 6.84 (d, 1H); 7.90 (s, 1H);
7.91 (d, 1H).

8B Ethyl 2-(3-phenylpropyl)-2.3-dihydrobenzofuran-5-car-boxylate

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Following the process described in example 3 (point ethylbenzene, the title compound was prepared, which was 4.29 (q, 2H); 4.74 (m, 1H); 6.70 (d, 1H); 7.10-7.29 $^{1}\mathrm{H}$ N.M.R. (300 MHz, CDCl $_{3}$) 6 ppm: 1.31 (t, 3H); 1.60silica gel column, 2-trifluoromethanesulfonyloxy eluting with n-hexane:ethyl acetate, 95:5 (75% yield). and 1.83 (m, 4H); 2.60 (t, 2H), 2.73 (dd, 1H); methy1-2,3-dihydrobenzofuran-5-carboxylate ಥ purified by chromatography through ethyl from starting 1H);

M

8C_2-(3-Phenylpropyl)-2,3-dihydrobenzofuran-5-carboxylicacid

(sc, 5H); 7.80 (s, 1H); 7.82 (d, 1H).

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Following the process described in example 6 (point E), starting from ethyl 2-(3-phenylpropyl)-2,3-dihydro-benzofuran-5-carboxylate, the title compound was prepared (98% yield).

1H N.M.R. (300 MHz, CD₃OD) 8 ppm: 1.60-1.85 (m, 4H);

2.62 (t, 2H), 2.76 (dd, 1H); 3.21 (dd, 1H); 4.78 (m, 1H); 6.65 (d, 1H); 7.10-7.29 (sc, 5H); 7.81 (sc, 2H).

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8D N-(3-Acetyl-2-hydroxyphenyl)-2-(3-phenylpropyl)-2.3-dihydrobenzofuran-5-carboxamide

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Following the process described in example 1 (point K), starting from 2-(3-phenylpropyl)-2,3-dihydrobenzofuran-5-carboxylic acid and 3-amino-2-hydroxyacetophenone, the title compound was prepared (60% yield).

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1H N.M.R. (300 MHz, CDCl₃) 6 ppm: 1.60-1.85 (m, 4H); 2.55 (s, 3H); 2.63 (t, 2H); 2.80 (dd, 1H); 3.22 (dd, 1H); 4.79 (m, 1H); 6.71 (d, 1H); 6.86 (t, 1H); 7.11-7.25 (sc, 5H); 7.38 (d, 1H); 7.62 (d, 1H); 7.64 (s, 1H); 8.34 (s, 1H); 8.66 (d, 1H). 8E Ethyl 8-[2-(3-phenylpropyl)-2.3-dihydrobenzofuran-5-

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carboxamidol-4-oxo-4H-1-benzopyran-2-carboxylate

Following the process described in example 1 (point A), starting from N-(3-acetyl-2-hydroxyphenyl)-2-(3-phenylpropyl)-2,3-dihydrobenzofuran-5-carboxamide and diethyl oxalate, the title compound was prepared, which was purified by crystallization in hot ethanol (67% yield).

S

1H N.M.R. (300 MHz, CDCl₃) & ppm: 1.45 (t, 3H); 1.70-1.92 (m, 4H); 2.71 (t, 2H); 2.93 (dd, 1H); 3.38 (dd, 1H); 4.50 (q, 2H); 4.93 (m, 1H); 6.85 (d, 1H); 7.16 (s, 1H); 7.18-7.32 (sc, 5H); 7.47 (t, 1H); 7.77 (dd, 1H); 7.84 (s, 1H); 7.87 (dd, 1H); 8.71 (s, 1H); 8.93 (dd, 1H).

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8F 8-[2-(3-Phenylpropyl)-2.3-dihydrobenzofuran-5-carbo-xamidol-4-oxo-4H-1-benzopyran-2-carboxylic acid

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Following the process described in example 1 (point M), starting from ethyl 8-[2-(3-phenylpropyl)-2,3-di-hydrobenzofuran-5-carboxamido]-4-oxo-4H-1-benzopyran-2-carboxylate, the title compound was prepared as a yellow solid with melting point 184-185°C, which was purified by digestion in methanol (41% yield).

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1H N.M.R. (300 MHz, DMSO) 6 ppm: 1.65-1.85 (m, 4H); 2.68
(t, 2H); 2.91 (dd, 1H); 3.38 (dd, 1H); 4.95 (m, 1H);
6.88 (d, 1H); 6.94 (s, 1H); 7.15-7.32 (sc, 5H); 7.54 (t, 1H); 7.83 (dd, 1H); 7.88 (m, 2H); 8.07 (dd, 1H); 10.01
(s, 1H).

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Example 9: N-[4-0xo-2-(1H-5-tetrazoly])-4H-1-benzopyran-8-yll-2-(3-phenylpropyl)-2.3-dihydrobenzofuran-5-carbo-xamide

9A N-[4-0x0-2-carbamov]-4H-1-benzopyran-8-yl]-2-(3-phenylpropyl)-2.3-dihydrobenzofuran-5-carboxamide

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Following the process described in example 7 (point A), starting from ethyl 8-[2-(3-phenylpropyl)-2,3-dihydrobenzofuran-5-carboxamido]-4-oxo-4<math>H-1-benzopyran-2-carboxylate, the title compound was prepared (quantitative yield).

S

7.55 (t, <u>ש</u> 8.30 4H); (s, 1H); 6.88 (d, 1H); 7.15-7.32 (sc, 5H); 4.95 DMSO) 6 ppm: 1.65-1.85 (m, 1H); 2.91 (dd, 1H); 3.38 (dd, 1H); ທີ 8.24 (broad 3H); 1H). 1H N.M.R. (300 MHz, 7.82-7.95 (m, 8.75 (broad s, 2H); 1H);

9B N-[4-0xo-2-cyano-4H-1-benzopyran-8-v]]-2-(3-phenyl-propyl)-2.3-dihydrobenzofuran-5-carboxamide

of the title compound was prepared, which was (point starting from N-[4-oxo-2-carbamoy1-4H-1-benzopyranmixtures example 2 silica gel 8-yl]-2-(3-phenylpropyl)-2,3-dihydrobenzofuran-5ether described in purified by chromatography through a ether:ethyl increasing polarity (55% yield). Following the process petroleum eluting with carboxamide,) (Q

12

1H N.M.R. (300 MHz, CDCl₃) 6 ppm: 1.70-1.95 (m, 4H);
2.71 (t, 2H); 2.90 (dd, 1H); 3.34 (dd, 1H); 5.00 (m,
1H); 6.80 (s, 1H); 6.84 (d, 1H); 7.15-7.32 (sc, 5H);
7.48 (t, 1H); 7.70 (d, 1H); 7.74 (s, 1H); 7.86 (d, 1H);
8.32 (s, 1H); 8.80 (d, 1H).

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25 9C_N-[4-0xo-2-(1H-5-tetrazolyl)-4H-1-benzopyran-8-yl]-2-(3-phenylpropyl)-2.3-dihydrobenzofuran-5-carboxamide

Following the process described in example 7 (point C), starting from N-[4-oxo-2-cyano-4*H*-1-benzopyran-8-y1]-2-(3-phenylpropyl)-2,3-dihydrobenzofuran-5-carboxamide, the title compound was prepared as a yellowish

234-235°C, which was

solid with melting point

in methanol:dichloromethane mixtures crystallization (61% yield).

2.66 (m, 1H); 7.87 (dd, 1H); 7.90 (d, 1H); 7.92 (s, 1H); 8.24 6.90 (d, 1H); 7.14 (s, 1H); 7.15-7.32 (sc, 5H); 7.56 (t, ¹H N.M.R. (300 MHz, DMSO) & ppm: 1.65-1.85 (m, 4H); 2.92 (dd, 1H); 3.39 (dd, 1H); 4.96 (dd, 1H); 9.98 (s, 1H). 2H);

S

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Example 10: 8-(2-Benzylthiomethyl-2.3-dihydrobenzofuran-2-benzylthiomethyl-2.3-dihydrobenzofuran-2-5-carboxamido)-4-oxo-4H-1-benzopyran-2-carboxylic acid Ethyl carboxylate 10A

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ところ A solution of benzylmercaptan (0.992 ml, 8.47 mmol) 5-carboxylate (3.00 g, 8.47 mmol) in ethanol (15 ml) was off under reduced pressure, the resulting combined organic phases were dried and the solvent was evaporated trifluoromethanesulfonyloxymethyl-2,3-dihydrobenzofuranunder inert atmosphere water (50 aqueous phase of 12.7 mmol) in absolute ethanol (10 ml). After 15 room temperature for 24 h. After that the volatiles a solution of ¹H N.M.R. (300 MHz, CDCl₃) & ppm: 1.34 (t, 3H); title compound as a dark oil (quantitative yield). reduced pressure, to obtain 2.810 g The solution of potassium hydroxide added. The resulting mixture was left under extracted with ethyl acetate (3x40 ml). residue was partitioned in a mixture of the stirring at room temperature, and in absolute ethanol (10 ml) and ethyl acetate (50 ml) added with a evaporated under

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2-Benzylthiomethyl-2.3-dihydrobenzofuran-2-carboxy-10B

potassium title 2-benzylthiomethyl-2,3-dihydrostirring for 3 h, after that was neutralized with 1M HCl The organic phase was dried and the solvent was evaporated off under refluxed under water (30 ml) the 8.53 mmol) in of 1M reduced melting point of ml). hydroxide (42.6 ml). The mixture was Ø solution 2.172 under acetate (4x30 The resulting crude was suspended in Ď off solid with to obtain benzofuran-2-carboxylate (2.70 ಡ evaporated added with solution of ethyl ethy1 brown pressure, ethanol was extracted with (100 ml) was ιď S S (85% yield). compound reduced

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2.81 6.80 (d, 1H); 7.20-7.27 (sc, 5H); 7.89 (s, 2.70 (dd, 1H); (dd, 1H); 3.02 (dd, 1H); 3.32 (dd, 1H); 1H N.M.R. (300 MHz, CDCl3) 8 ppm: 1H); 7.97 (d, 1H). (m, 1H);

H 2

10C N-(3-Acetyl-2-hydroxyphenyl)-2-benzylthiomethyl-2.3dihydrobenzofuran-5-carboxamide

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starting from 2-benzylthiomethyl-2,3-dihydrobenzofu-3-amino-2-hydroxyacetophenone, Š column, eluting purified solid Following the process described in example 1 a yellow Was acetate, 90:10 (86% yield). point 119-121°C, which chromatography through a silica gel the title compound was prepared as acid and ran-2-carboxylic n-hexane:ethyl melting

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1H); 1H); 3H); 6.83 (d, 1H); 6.93 (t, (dd, 1H); 3.34 (dd, 7.72 (d, 1H); 2.61 : mdd 7.21-7.35 (sc, 5H); 7.46 (d, 1H); 2.80 (dd, 1H); 3.06 (300 MHz, CDC1₃) 8 4.95 (m, 1H); 3H); 1H N.M.R. (dd, 1H); 3.79 (s,

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1H);

(dd,

1H);

3.78 (s, 2H); 4.31 (q, 2H); 4.92 (m, 1H); 6.76 (d,

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7.19-7.27 (sc, 5H); 7.82 (s, 1H); 7.86 (dd, 1H)

(dd, 1H); 2.77 (dd, 1H); 2.98 (dd, 1H); 3.25

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H); 8.53 (s, 1H); 8.74 (d, 1H).

10D Ethyl 8-(2-benzylthiomethyl-2,3-dihydrobenzofuran-5-carboxamidol-4-oxo-4H-1-benzopyran-2-carboxylate

and from N-(3-acetyl-2-hydroxyphenyl)-2-bendiethyl oxalate, the title compound was prepared as a (point solid with melting point 175-177°C, a silica example 1 zylthiomethyl-2,3-dihydrobenzofuran-5-carboxamide gel column, eluting with chloroform (81% yield). through described in which was purified by chromatography the process slightly yellow Following starting

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1H N.M.R. (300 MHz, CDCl₃) 6 Ppm: 1.47 (t, 3H); 2.72
(dd, 1H); 2.34 (dd, 1H); 3.09 (dd, 1H); 3.38 (dd, 1H);
3.80 (s, 3H); 4.49 (q, 2H); 4.99 (m, 1H); 6.85 (d, 1H);
7.12 (s, 1H); 7.21-7.35 (sc, 5H); 7.43 (t, 1H); 7.76 (d, 1H); 7.80 (s, 1H); 7.85 (d, 1H); 8.70 (s, 1H); 8.89 (d, 1H).

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10E 8-(2-Benzylthiomethyl-2.3-dihydrobenzofuran-5-carbo-xamido)-4-oxo-4H-1-benzopyran-2-carboxylic acid

Following the process described in example 1 (point M), starting from ethyl 8-(2-benzylthiomethyl-2,3-dihy-drobenzofuran-5-carboxamido)-4-oxo-4*H*-1-benzopyran-2-carboxylate, the title compound was prepared as a yellow solid with melting point 122-125°C (81% yield).

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1H N.M.R. (300 MHz, DMSO) & ppm: 2.80 (d, 2H); 3.05 (dd,
1H); 3.20 (dd, 1H); 3.85 (s, 3H); 5.08 (m, 1H); 6.91 (s,
1H); 6.92 (d, 1H); 7.27 (m, 1H); 7.34 (d, 4H); 7.54 (t,
1H); 7.86 (d, 1H); 7.88 (d, 1H); 7.90 (s, 1H); 8.08 (dd,
1H); 10.04 (s, 1H).

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Example 11: 8-[2-(4'-Fluorobenzyloxymethyl)-2.3-dihydro-benzofuran-5-carboxamidol-4-oxo-4H-1-benzopyran-2-carbo-xylic acid

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11A Ethyl 2-(4'-fluorobenzyloxymethyl)-2,3-dihydrobenzofuran-2-carboxylate

2-hydroxymethyl-2,3-dihydrobeneluting with purified example 1 gel column, prepared, which was zofuran-5-carboxylate and 4'-fluorobenzyl acetate, 95:5 (68% yield). Following the process described in a silica ethyl chromatography through compound was from n-hexane:ethyl starting title

S

2.99 1H); 3H); (dd , (q, 2H); 4.52 (dd, 2H); 5.03 (m, 1H); 6.79 (d, 2H); 7.26 (dd, 2H); 7.83 (s, 1H); 7.87 3.68 Ppm: 1.34 (t, (dd, 1H); (dd, 1H); 3.23 (dd, 1H); 3.62 $CDCl_3$) 8 MHZ, ¹H N.M.R. (300 7.00 4.30 1H).

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11B 2-(4'-Fluorobenzyloxymethyl)-2.3-dihydrobenzofuran-2-carboxylic acid

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Following the process described in example 6 (point E), starting from ethyl 2-(4'-fluorobenzyloxymethyl)-2,3-dihydrobenzofuran-2-carboxylate, the title compound was prepared, which was purified by crystallization in methanol (94% yield).

1H N.M.R. (300 MHz, CDCl₃) & ppm: 3.01 (dd, 1H); 3.27
(dd, 1H); 3.65 (m, 2H); 4.58 (dd, 2H); 5.05 (m, 1H);
6.81 (d, 1H); 7.00 (t, 2H); 7.27 (dd, 2H); 7.86 (s, 1H);
7.92 (dd, 1H); 12.20 (broad signal, 1H).

25 11C N-(3-Acetyl-2-hydroxyphenyl)-2-(4'-fluorobenzyloxy-methyl)-2,3-dihydrobenzofuran-5-carboxamide

title compound 2-(4'-fluorobenzyloxymethyl)-2,3-Following the process described in example 1 eluting the λq acid, purified column, dihydrobenzofuran-2-carboxylic Was gel from which silica starting prepared

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hexane:chloroform, 1:1 (81% yield).

3.05 2H); (dd, 3H); ZH); 4.58 2.60 (s, (300 MHz, CDCl₃) 6 ppm: (dd, 1H); 3.65 (m, 3.30 1H); 1H N.M.R.

2H); (m, 1H); 6.84 (d, 1H); 6.92 (t, 1H); 7.01 (t,

1H); 7.73 (s, 7.27 (m, 2H); 7.43 (d, 1H); 7.71 (d, 1H); (s, 1H); 8.71 (d, 1H); 12.96 (s, 1H).

M

8-[2-(4'-fluorobenzyloxymethyl)-2.3-dihydrobenzofuran-5-carboxamidol-4-oxo-4H-1-benzopyran-2-carbo-Ethyl xylate 110

0

Was Following the process described in example 1 (point silica gel column, eluting with n-hexane:chloroform, 1:2 from N-(3-acetyl-2-hydroxyphenyl)-2-(4'prepared, which was purified by chromatography through a fluorobenzyloxymethyl)-2,3-dihydrobenzofuran-5-carboxacompound title the oxalate, diethyl starting (53% yield). and A),

₹-j

3.10 2H); 2H); 8-[2-(4'-Fluorobenzyloxymethyl)-2.3-dihydrobenzofu-(s, 1H); 7.30 (m, 2H); 7.44 (t, 1H); 7.77 (dd, 1H); 7.83 (s, 1H); 7.87 (d, 1H); 8.71 (s, 1H); 8.90 (d, 1H). ran-5-carboxamidol-4-oxo-4H-1-benzopyran-2-carboxylic (ð) ¹H N.M.R. (300 MHz, CDCl₃) & ppm: 1.46 (t, 3H); (dd, 2H); 5.10 (m, 1H); 6.88 (d, 1H); 7.01 (t, 4.49 2H); 3.35 (dd, 1H); 3.70 (m, (dd, 1H); 7.13

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Following the process described in example 1 (point starting from ethyl 8-[2-(4'-fluorobenzyloxymethyl)as 2,3-dihydrobenzofuran-5-carboxamido)-4-oxo-4*H*-1-benzopy which prepared 195-197°C, the title compound was purified by crystallization in methanol. solid with melting point 1H N.M.R. (300 MHz, DMSO) 6 ran-2-carboxylate, yellow £

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2H); 5.12 (m, 1H); (sc, 3H); 8.08 (dd, 1H); 10.03 (s, 7.38 (t, 2H); 2H); 2H); 4.56 (s, 7.17 (t, 1H); 3.68 (d, (8) 6.95 7.88 (dd, 1H); 1H);

N-[4-0xo-2-(1H-5-tetrazoly1)-4H-1-benzopyran-8-y11-2-(4'-fluorobenzyloxymethyl)-2,3-dihydrobenzofuran-5-carboxamide Example

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N-[4-0xo-2-carbamoyl-4H-1-benzopyran-8-v1]-2-(4'fluorobenzyloxymethyl)-2.3-dihydrobenzofuran-5-carboxa-

dry ethyl 8-[2-(4'-fluorobenzyloxyme-E compound solvents thyl)-2,3-dihydrobenzofuran-5-carboxamido]-4-oxo-4H-1 in resulting mixture (12 mmo]) 4 h, then the g of the title methano1 2.36 -20°C was מ ļ solution). The benzopyran-2-carboxylate (1.219 stirring at 0°C for obtain 1.158 at solution (100 ml) solution of ammonia approximately 4M removed, to tetrahydrofuran saturated under 10 1

1H); 1H N.M.R. (300 MHz, DMSO) & ppm: 3.09 (dd, (quantitative yield).

6.87 7.53 8.38 2H); 1H); 1H); 5.11 (m, 6.92 (d, 1H); 7.18 (t, 2H); 7.38 (t, 'n 8.60 (broad s, 1H); 10.25 (s, 1H). 3.67 (s, 2H); 4.56 (s, 2H); (broad 3H); 8.25 7.84 (sc, 1H); 1H); (s, 1H); 1H);

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N-F4-0xo-2-cyano-4H-1-benzopyran-8-yll-2-(4'-fluorobenzyloxymethyl)-2.3-dihydrobenzofuran-5-carboxamide

25

Yas reacting N-[4-oxo-2-carbamoyl-4H-1-benzopyran-8column, yl]-2-(4'-fluorobenzyloxymethyl)-2,3-dihydrobenzofuranat 0°C, the title compound was prepared, which Following the process described in example 2 gel by chromatography through a silica 5-carboxamide with phosphorous oxychloride purified D), by 0.5 h

30

3.37

1H);

(dd ,

ppm: 3.10

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with

1:1 ether:chloroform, petroleum eluting yield). 3.33

1H);

(dđ,

3.10

1н м.м.к. (300 мнг, сосі_з) 8 ррт:

1H);

(H) (s, 1H); 6.89 (d, 1H); 7.02 (t, 2H); 7.38 (m, 5.10 (dd, 1H); 3.70 (m, 2H); 4.59 (dd, 2H);

S

2H); 1H); 7.48 (t, 1H); 7.72 (dd, 1H); 7.78 (s, 1H); 7.88 (d,

8.35 (s, 1H); 8.79 (d, 1H).

N-[4-0xo-2-(1H-5-tetrazolyl)-4H-1-benzopyran-8-vl]-2-(4'-fluorobenzyloxymethyl)-2.3-dihydrobenzofuran-5-120

carboxamide

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Was Following the process described in example 7 (point from N-[4-oxo-2-cyano-4H-1-benzopyran-8-Yl]-2-(4'-fluorobenzyloxymethyl)-2,3-dihydrobenzofuran-S white solid with melting point 229-232°C, which prepared purified by digestion in ethyl ether (77% yield). compound was title 5-carboxamide, the starting

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1H); 2H); 1H); (dd, 1H); 6.93 (d, 1H); 7.05 (t, 2H); 7.25 (s, 1H); 7.33 (m, 7.52 (t, 1H); 7.89 (d, 1H); 7.92 (s, 1H); 7.96 (dd, 2H); 4.60 (dd, 2H); 5.12 (m, ¹H N.M.R. (300 MHz, DMSO) 8 ppm: 3.12 (d, 1H); 10.05 (s, 1H). (dd, 1H); 3.72 (d,

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8-[7-Chloro-2-(3-phenylpropyl)-2,3-dihydrobenzofuran-5-carboxamidol-4-oxo-4H-1-benzopyran-2-carbo-13: xylic acid

13A Methyl 3-chloro-4-hydroxybenzoate 25

the example 5 (point 3-chloro-4-hydroxybenzoic acid, Following the process described in title compound was prepared (87% yield). from starting

¹H N.M.R. (300 MHz, CDCl₃) & PPm: 1.39 (t, 3H); 4.37 (q,

8.06 (d, 1H). 2H); 7.04 (d, 1H); 7.89 (dd, 1H); 30

13B Ethyl 4-allyloxy-3-chlorobenzoate

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the ethyl 3-chloro-4-hydroxybenzoate, φ example process described in yield). prepared (91% Following the from title compound was starting

6.07 ¹H N.M.R. (300 MHz, CDCl₃) 5 ppm: 1.39 (t, 3H); 4.37 (q, 4.69 (d, 2H); 5.35 (dd, 1H); 5.49 (dd, 1H); (m, 1H); 6.94 (d, 1H); 7.91 (dd, 1H); 8.07 (d, 1H)

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13C Ethyl 3-allyl-5-chloro-4-hydroxybenzoate

DX DX (point starting from ethyl 4-allyloxy-3-chlorobenzoate, purified example 6 (0.2 which was pressure described prepared, reduced process compound was (quantitative yield). distillation under Following the

10

(g, 3.45 6.01 3H); 1H); ¹H N.M.R. (300 MHz, CDCl₃) 8 ppm: 1.38 (t, 5.09 (d, 1H); 5.14 (d, 7.92 (d, 1H). (q, 2H); (d, 1H); 4.35 7.76 2H); 1H);

5

Ethyl 7-chloro-2-hydroxymethyl-2,3-dihydrobenzofuran-5-carboxylate 130

3-ally1-5-chloro-4-hydroxybenzoate, the title compound was prepared (80% yield). Following the process described in example 6 from ethyl starting

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3.19 3.97 (dd, 1H); 13E Ethyl 7-chloro-2-trifluoromethanesulfonyloxymethyl ¹H N.M.R. (300 MHz, CDCl₃) 8 ppm: 1.37 (t, 3H); 1H); 7.85 (d, 3.78 (dd, 1H); (q, 2H); 5.09 (m, 1H); 7.74 (d, (dd, 1H); 3.33 1H);

2.3-dihydrobenzofuran-5-carboxylate 25

(point 7-chloro-2-hydroxymethyl-2,3compound Following the process described in example 3 title the dihydrobenzofuran-5-carboxylate, prepared (quantitative yield). from ethyl starting) (V

3.20 1H); 3H); (dd , 4.67 1.38 (t, 2H); : mdd <u>(</u>d) 1H); 4.32 CDC13) 8 MHZ, (đđ, (300 3.53 1H N.M.R. (dd, 1H);

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4.77 (dd, 1H); 5.28 (m, 1H); 7.76 (d, 1H); 7.88 (d, 1H).

13F Ethyl 7-chloro-2-(3-phenylpropyl)-2,3-dihydrobenzo-furan-5-carboxylate

Following the process described in example 3 (point B), starting from ethyl 7-chloro-2-trifluoromethanesulfonyloxymethyl-2,3-dihydrobenzofuran-5-carboxylate and 2-bromoethylbenzene, the title compound was prepared, which was purified by chromatography through a silica gel column, eluting with petroleum ether:ethyl acetate, 95:5 (58% yield).

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1H N.M.R. (300 MHz, CDCl₃) 5 ppm: 1.36 (t, 3H); 1.70-1.92 (m, 4H); 2.68 (t, 2H), 2.91 (dd, 1H); 3.34 (dd, 1H); 4.32 (q, 2H); 4.95 (m, 1H); 7.15-7.30 (sc, 5H); 7.71 (d, 1H); 7.86 (d, 1H).

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15 13G 2-(3-Phenylpropyl)-2.3-dihydrobenzofuran-5-carboxy-lic acid

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Following the process described in example 6 (point E), starting from ethyl 7-chloro-2-(3-phenylpropyl)-2,3-dihydrobenzofuran-5-carboxylate, the title compound was prepared (92% yield).

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1H N.M.R. (300 MHz, CD₃OD) 6 ppm: 1.70-1.92 (m, 4H);
2.70 (t, 2H), 2.95 (dd, 1H); 3.40 (dd, 1H); 4.99 (m, 1H); 7.15-7.30 (sc, 5H); 7.73 (d, 1H); 7.,83 (d, 1H).

13H N-(3-Acetyl-2-hydroxyphenyl)-7-chloro-2-(3-phenyl-propyl)-2.3-dihydrobenzofuran-5-carboxamide

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Following the process described in example 1 (point K), starting from 7-chloro-2-(3-phenylpropyl)-2,3-dihy-drobenzofuran-5-carboxylic acid, the title compound was prepared, which was purified by chromatography through a silica gel column, eluting with petroleum ether:chloroform, 1:1 (84% yield).

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α, 4,

4H); 1H); 5H); 3.24 CDCl₃) 6 ppm: 1.60-1.88 (m, 7.45 (s, 1H); 7.63 (s, 1H); 8.38 (s, 7.11-7.25 (dd, 1H); 2.82 6.79 (t, 1H); 2.63 (t, 2H); (300 MHz, 4.84 (m, 1H); 3H); 7.29 (d, 1H); 8.58 (d, 1H). 1H);

131 Ethyl 8-[7-chloro-2-(3-phenylpropyl)-2,3-dihydroben-zofuran-5-carboxamidol-4-oxo-4H-1-benzopyran-2-carboxy-late

Following the process described in example 1 (point A), starting from N-(3-acetyl-2-hydroxyphenyl)-7-chloro-2-(3-phenylpropyl)-2,3-dihydrobenzofuran-5-carboxamide, the title compound was prepared, which was purified by chromatography through a silica gel column, eluting with petroleum ether:chloroform mixtures of increasing polarity (57% yield).

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1H N.M.R. (300 MHz, CDCl₃)u & ppm: 1,47 (t, 3H); 1.761.96 (m, 4H); 2.72 (t, 2H); 3.01 (dd, 1H); 3.44 (dd,
1H); 4.51 (q, 2H); 5.03 (m, 1H); 7.16 (s, 1H); 7.19-7.33
(sc, 5H); 7.47 (t, 1H); 7.71 (s, 1H); 7.79 (s, 1H); 7.89

13J 8-[7-Chloro-2-(3-phenylpropyl)-2.3-dihydrobenzofu-ran-5-carboxamidol-4-oxo-4H-1-benzopyran-2-carboxylicacid

8.66 (s, 1H); 8.88 (dd, 1H)

1H);

(**d**d ,

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Following the process described in example 1 (point M), starting from ethyl 8-[7-chloro-2-(3-phenylpropyl)-2,3-dihydrobenzofuran-5-carboxamido]-4-oxo-4*H*-1-benzopyran-2-carboxylate, the title compound was prepared as a white solid with melting point 224-225°C, which was purified by chromatography through a silica gel column, eluting with chloroform:methanol, 98:2 (54% yield).

23

5 ppm:

¹H N.M.R. (300 MHz, CD₃OD/CDCl₃ mixtures)

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5H); 7.50 (t, 1H); 7.74 (d, 1H); 7.85 (d, 1H); 7.94 (dd, 1H); 3.46 (sc, 5.04 (m, 1H); 7.15 (s, 1H); 7.19-7.32 3.02 (dd, 1H); 2.73 (t, 2H); 82 4H); 8.53 (dd, 1H). (m) 1H);

Example 14: 8-[2-(3-Phenylpropyl)-2.3-dihydrobenzofuran-5-carboxamidol-6-fluoro-4-oxo-4H-1-benzopyran-2-carboxy-

S

14A 4-Fluorophenyl acetate

Following the process described in example 1 (point starting from 4-fluorophenol, the title compound was prepared as a colourless oil (94% yield). G),

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3H); 7.06 (d, ¹H N.M.R. (300 MHz, CDCl₃) 6 ppm: 2.29 (s,

14B 5-Fluoro-2-hydroxyacetophenone

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Following the process described in example 1 (point acetate, the title solid with melting petroleum chromatography with purified by silica gel column, eluting prepared as a white starting from 4-fluorophenyl ether:chloroform, 9:1 (78% yield). which was point 55-58°C, compound was through a

6.95 (dd, 1H); 7.22 (dt, 1H); 7.40 (dd, 1H); 11.98 (s, 1H). 3H); ¹H N.M.R. (300 MHz, CDCl₃) 6 ppm: 2.62 (s,

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14C 5-Fluoro-2-hydroxy-3-nitroacetophenone

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- Following the process described in example 1 (point title compound was prepared as a yellow solid which was silica gel column, I), starting from 5-fluoro-2-hydroxyacetophenone, ether:chloroform, purified by chromatography through a petroleum with eluting
- 7.81 3H); ¹H N.M.R. (300 MHz, CDCl₃) 6 ppm: 2.72 (s, (dd, 1H); 7.96 (d, 1H); 12.62 (s, 1H) 30

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14D_3-Amino-5-fluoro-2-hydroxyacetophenone

5-fluoro-2-hydroxy-3-nitroacetophe-(quantitative described in example 1 prepared MASS title compound Following the process from starting yield): none,

S

3H); 2.55 : mdd ω (300 MHz, CD₃OD) 7.84 (dd, 1H). 1H); 1H N.M.R.

N-(3-Acetyl-5-fluoro-2-hydroxyphenyl)-2-(3-phenylpropyl)-2.3-dihydrobenzofuran-5-carboxamide

10

Was starting from 2-(3-phenylpropyl)-2,3-dihydrobenzofuran-5-carboxylic acid and 3-amino-5-fluoro-2-hydroxyace was prepared, which Following the process described in example 1 silica gel with petroleum ether:chloroform, purified by chromatography through compound title tophenone, the eluting yield). K),

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4H); 5H); (dd, 1H); 7.40 (d, 1H); 7.62 (d, 1H); 7.65 (s, 1H); 8.19 (s, (300 MHz, CDCl₃) 8 ppm: 1.70-1.95 (m, 1H); 7.11-7.25 (dd, 6.72 (d, 1H); 2.70 (t, 2H); 2.89 4.79 (m, 1H); 3H); 1H N.M.R.

8-[2-(3-phenylpropyl)-2.3-dihydrobenzofuran-5carboxamidol-6-fluoro-4-oxo-4H-1-benzopyran-2-carboxyla-Ethyl te

25

8.66 (d, 1H).

20

Following the process described in example 1 (point starting from N-(3-acetyl-5-fluoro-2-hydroxyphenyl)prepared, 2-(3-phenylpropyl)-2,3-dihydrobenzofuran-5-carboxamide ethanol Was which was purified by crystallization in compound title oxalate, the diethyl yield). A),

 $CDC1_3$) 6 ppm: 1.48 (t, ¹H N.M.R. (300 MHz,

87

1.92 (m, 4H); 2.79 (t, 2H); 2.90 (dd, 1H); 3.32 (dd, 1H); 4.48 (q, 2H); 4.90 (m, 1H); 6.80 (d, 1H); 7.08 (s, 1H); 7.18-7.32 (sc, 5H); 7.42 (dd, 1H); 7.69 (dd, 1H); 7.77 (s, 1H); 8.70 (dd, 1H); 8.71 (s, 1H).

14G 8-[2-(3-Phenylpropyl)-2.3-dihydrobenzofuran-5-carbo-xamidol-6-fluoro-4-oxo-4H-1-benzopyran-2-carboxylic acid

S

Following the process described in example 1 (point M), starting from ethyl 8-[2-(3-phenylpropyl)-2,3-di-hydrobenzofuran-5-carboxamido]-6-fluoro-4-oxo-4*H*-1-benzopyran-2-carboxylate, the title compound was prepared as a white solid with melting point 183-185°C, which was purified by chromatography through a silica gel column, eluting with chloroform:methanol, 95:5 (66% yield).

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1H N.M.R. (300 MHz, DMSO) & ppm: 1.65-1.85 (m, 4H); 2.64
(t, 2H); 2.87 (dd, 1H); 3.31 (dd, 1H); 4.91 (m, 1H);
6.83 (d, 1H); 6.87 (s, 1H); 7.15-7.32 (sc, 5H); 7.49
(dd, 1H); 7.80 (d, 1H); 7.82 (s, 1H); 8.14 (dd, 1H);
10.17 (s, 1H).

1

Example 15: 8-[4-Chloro-2-(3-phenylpropyl)-2.3-dihydro-benzofuran-5-carboxamidol-4-oxo-4H-1-benzopyran-2-carbo-xylic acid

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15A 4-Allyloxy-2-chlorobenzonitrile

Pollowing the process described in example 6 (point A), starting from 2-chloro-4-hydroxybenzonitrile, the title compound was prepared as a white solid with melting point 50-52°C (98% yield).

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1H N.M.R. (300 MHz, CDCl₃) & ppm: 4.59 (m, 2H); 5.35
(dd, 1H); 5.40 (dd, 1H); 6.00 (m, 1H); 6.88 (dd, 1H);
7.03 (d, 1H); 7.59 (d).

30 15B 5-Allyl-2-chloro-4-hydroxybenzonitrile and 3-allyl-2-chloro-4-hydroxybenzonitrile

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eluting with 6 (point the isomer 5-ally1-2-chloro-4-hydroxybenisomer 3-ally1-2separated by chromatography through 5-ally1-2-chloro-4-hydroxybenzonitrile and 4-allyloxy-2-chlorobenzonitrile, obtained. example petroleum recovered and ally1-2-chloro-4-hydroxybenzonitrile was described in petroleum ether:ethyl ether, 6:4, the Eluting with zonitrile (39% yield) was Following the process column. from isomers were 8:2, gel mixture of silica two

S

(ď, chloro-4-hydroxybenzonitrile was recovered (51% yield). 7.44 <u>.:</u> 1H); (isomer (s) 1H); 7.03 e ppm CDC13) (m, 2H); 5.98 (m, (300 MHz, 5.12-5.28 N.M.R. 1H). 1_H

1H N.M.R. (300 MHz, CDCl₃) & ppm (isomer 3): 3.61 (d, 5.07-5.18 (m,2H); 5.95 (m, 1H); 6.86 (d, 1H); 7.46 (d, 1H);

15

15C 4-Chloro-2-hydroxymethyl-2.3-dihydrobenzofuran-5-carbonitrile

3.32 Following the process described in example 6 (point 1H); 3-ally1-2-chloro-4-hydroxybenzoni-(dd, 1H); 5.08 (m, trile, the title compound was prepared (92% yield). 3.14 3.91 (dd, 1H); CDC13) 6 ppm: 1H); (d, 1H); 7.41 (d, 1H). from ¹H N.M.R. (300 MHz, (đđ, 3.79 starting 1H); (dď, ີ່ (ບ

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25 15D 4-Chloro-2-trifluoromethanesulfonyloxymethyl-2.3-di-hydrobenzofuran-5-carbonitrile

Following the process described in example 3 (point A), starting from 4-chloro-2-hydroxymethyl-2,3-dihydro-benzofuran-5-carbonitrile, the title compound was prepared (64% yield).

¹H N.M.R. (300 MHz, CDCl₃) 6 ppm: 3.19 (dd, 1H); 3.50

83

(dd, 1H); 4.68 (dd, 1H); 4.70 (dd, 1H); 5.30 (m, 1H); 6.81 (d, 1H); 7.50 (d, 1H).

15E 4-Chloro-2-(3-phenylpropyl)-2.3-dihydrobenzofuran-5carbonitrile

S

ether, Following the process described in example 3 (point starting from 4-chloro-2-trifluoromethanesulfonylo-2prepared, silica N column, eluting with petroleum ether:ethyl through compound was xymethyl-2,3-dihydrobenzofuran-5-carbonitrile chromatography the title which was purified by bromoethylbenzene, 95:5 (68% yield). B),

10

1H N.M.R. (300 MHz, CDCl₃) & ppm: 1.65-1.90 (m, 4H); 2.68 (t, 2H), 2.87 (dd, 1H); 3.12 (dd, 1H); 4.92 (m, 1H); 6.69 (d, 1H); 7.14-7.32 (sc, 5H); 7.40 (d, 1H).

15F 4-Chloro-2-(3-phenylpropyl)-2.3-dihydrobenzofuran-5-carboxylic acid

15

15

Following the process described in example 5 (point G), starting from 4-chloro-2-(3-phenylpropyl)-2,3-dihy-drobenzofuran-5-carbonitrile, the title compound was prepared (89% yield).

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1H N.M.R. (300 MHz, CDCl₃) & ppm: 1.65-1.90 (m, 4H);
2.70 (t, 2H), 2.91 (dd, 1H); 3,38 (dd, 1H); 4.93 (m, 1H); 6.69 (d, 1H); 7.14-7.32 (sc, 5H); 7.98 (d, 1H).

15G N-(3-Acetyl-2-hydroxyphenyl)-4-chloro-2-(3-phenyl-propyl)-2.3-dihydrohenzofuran-5-carboxamide

25

Following the process described in example 1 (point K), starting from 4-chloro-2-(3-phenylpropyl)-2,3-dihy-drobenzofuran-5-carboxylic acid and 3-amino-2-hydroxy-acetophenone, the title compound was prepared (938 yield).

1H N.M.R. (300 MHz, CDCl₃) 8 ppm: 1.60-1.85 (m, 4H);

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90 2.60 (s, 3H); 2.65 (t, 2H); 2.90 (dd, 1H); 3.32 (dd, 1H); 4.88 (m, 1H); 6.71 (d, 1H); 6.92 (t, 1H); 7.15-7.30 (sc, 5H); 7.43 (d, 1H); 7.67 (d, 1H); 8.75 (d, 1H); 8.80 (s, 1H); 12.92 (s, 1H).

15H_Ethyl_8-[4-chloro-2-(3-phenylpropyl)-2.3-dihydroben-zofuran-5-carboxamidol-4-oxo-4H-1-benzopyran-2-carboxy-late

S

Following the process described in example 1 (point A), starting from N-(3-acetyl-2-hydroxyphenyl)-4-chloro-2-(3-phenylpropyl)-2,3-dihydrobenzofuran-5-carboxamide and diethyl oxalate, the title compound was prepared, which was purified by chromatography through a silica gel column, eluting with petroleum ether:chloroform, 4:6 (61% yield).

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1H N.M.R. (300 MHz, CDCl₃) & ppm: 1.40 (t, 3H); 1.701.92 (m, 4H); 2.68 (t, 2H); 2.91 (dd, 1H); 3.35 (dd,
1H); 4.42 (q, 2H); 4.92 (m, 1H); 6.72 (d, 1H); 7.10 (s,
1H); 7.15-7.32 (sc, 5H); 7.40 (t, 1H); 7.85 (dd, 1H);
7.90 (d, 1H); 8.93 (d, 1H); 9.42 (s, 1H).

151 8-[4-Chloro-2-(3-phenylpropyl)-2,3-dihydrobenzofu-ran-5-carboxamidol-4-oxo-4H-1-benzopyran-2-carboxylic acid

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(m, 1H); 6.75 (d, 1H); 7.11 (s, 1H); 7.15-7.35 starting from ethyl 8-[4-chloro-2-(3-phenylpropyl)-(point 2,3-dihydrobenzofuran-5-carboxamido]-4-oxo-4H-1-benzopyprepared as solid which decomposes at 265°C (81% yield). 3.41 CD₃OD/CDCl₃ mixtures) & ppm: 7.48 (m, 2H); 7.94 (d, 1H); 8.79 (d, 1H). Following the process described in example 1 4H); 2.70 (t, 2H); 2.94 (dd, 1H); ran-2-carboxylate, the title compound was MHZ, (300 4.92 yellowish 5H); 1.92 (m, (sc,

46

Example 16: 8-[6-Chloro-2-(3-phenylpropyl)-2.3-dihydro-benzofuran-5-carboxamidol-4-oxo-4H-1-benzopyran-2-carbo-xylic acid

16A 6-Chloro-2-hydroxymethyl-2.3-dihydrobenzofuran-5-

carbonitrile

K)

Following the process described in example 6 (point C), starting from 5-allyl-2-chloro-4-hydroxybenzonitrile, the title compound was prepared, which was purified by chromatography through a silica gel column, eluting with petroleum ether:chloroform, 1:4 (79% yield).

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1H N.M.R. (300 MHz, CDCl3) & ppm: 3.10 (dd, 1H); 3.29
(dd, 1H); 3.77 (dd, 1H); 3.92 (dd, 1H); 5.08 (m, 1H);
6.88 (d, 1H); 7.41 (s, 1H).

16B 6-Chloro-2-trifluoromethanesulfonyloxymethyl-2.3-dihydrobenzofuran-5-carbonitrile

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Following the process described in example 3 (point A), starting from 6-chloro-2-hydroxymethyl-2,3-dihydro-benzofuran-5-carbonitrile, the title compound was prepared (76% yield).

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1H N.M.R. (300 MHz, CDCl₃) 6 ppm: 3.13 (dd, 1H); 3.49
(dd, 1H); 4.68 (dd, 1H); 4.69 (dd, 1H); 5.30 (m, 1H);
6.93 (s, 1H); 7.44 (s, 1H).

16C 6-Chloro-2-(3-phenylpropyl)-2.3-dihydrobenzofuran-5-carbonitrile

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Following the process described in example 3 (point B), starting from 6-chloro-2-trifluoromethanesulfonyloxymethyl-2,3-dihydrobenzofuran-5-carbonitrile and 2-bromoethylbenzene, the title compound was prepared, which was purified by chromatography through a silica gel column, eluting with petroleum ether:ethyl ether,

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9:1 (20% yield).

1H N.M.R. (300 MHz, CDCl₃) & ppm: 1.65-1.90 (m, 4H);
2.66 (t, 2H), 2.78 (dd, 1H); 3.23 (dd, 1H); 4.89 (m, 1H); 6.78 (d, 1H); 7.14-7.30 (sc, 6H).

16D 6-Chloro-2-(3-phenylpropyl)-2.3-dihydrobenzofuran-5carboxylic acid

S

Following the process described in example 5 (point G), starting from 6-chloro-2-(3-phenylpropyl)-2,3-dihy-drobenzofuran-5-carbonitrile, the title compound was prepared (77% yield).

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1H N.M.R. (300 MHz, CDCl₃) 6 ppm: 1.65-1.90 (m, 4H);
2.62 (m, 3H), 3.07 (m, 1H); 4.76 (m, 1H); 6.68 (s, 1H);
7.14-7.32 (sc, 5H); 7.71 (s, 1H).

16E N-(3-Acetyl-2-hydroxyphenyl)-6-chloro-2-(3-phenyl-propyl)-2.3-dihydrobenzofuran-5-carboxemide

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prepared, example 1 (point 6-chloro-2-(3-phenylpropyl)-2,3-dihy-acetate, purified by chromatography through hydroxyacetophenone, the title compound was described in column, eluting with hexane:ethyl acid Following the process drobenzofuran-5-carboxylic from starting which was gel

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7.30 4H); (HT 7.15-(q, Ě (300 MHz, CDC1₃) 6 ppm: 1.60-1.85 8.71 (m, 1H); 6.72 (d, 1H); 6.87 (t, 1H); 3H); 2.63 (t, 2H); 2.74 (dd, 1H); 7.38 (dd, 1H); 7.59 (s, 1H); (s, 1H). (s, 1H); 12.92 5H); 1H N.M.R. 4.80 (s) 1H); (sc,

2

16F Ethvl 8-[6-chloro-2-(3-phenylpropyl)-2,3-dihydroben-zofuran-5-carboxamidol-4-oxo-4H-1-benzopyran-2-carboxy-

Following the process described in example 1 (poin

A), starting from N-(3-acetyl-2-hydroxyphenyl)-6-chlorocompound was prepared, 2-(3-phenylpropyl)-2,3-dihydrobenzofuran-5-carboxamide diethyl oxalate, the title

gel column, eluting with petroleum ether:chloroform, 4:6 silica was purified by chromatography through a (75% yield).

M

¹H N.M.R. (300 MHz, CDCl₃) & ppm: 1.42 (t, 3H); 1.70-1.92 (m, 4H); 2.68 (t, 2H); 2.85 (dd, 1H); 3.29 (dd, 4.45 (q, 2H); 4.92 (m, 1H); 6.81 (s, 1H); 7.12 (s, 7.85 (dd, 1H); 1H); 7.15-7.32 (sc, 5H); 7.43 (t, 1H); (s, 1H); 8.93 (d, 1H); 9.52 (s, 1H).

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8-[6-Chloro-2-(3-phenylpropyl)-2.3-dihydrobenzofuran-5-carboxamidol-4-oxo-4H-1-benzopyran-2-carboxylic

Following the process described in example 1 (point M), starting from ethyl 8-[6-chloro-2-(3-phenylpropyl)-2,3-dihydrobenzofuran-5-carboxamido]-4-oxo-4H-1-benzopyran-2-carboxylate, the title compound was prepared as yellowish solid which decomposes at 265°C (78% yield).

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1H); 4.80 (m, 1H); 6.73 (s, 1H); 7.11 (s, 1H); 7.15-7.35 $^1\mathrm{H}$ N.M.R. (300 MHz, $\mathrm{CD}_3\mathrm{OD}/\mathrm{CDCl}_3$ mixtures) 6 ppm: 1.65-5H); 7.42 (t, 1H); 7.65 (s, 1H); 7.86 (dd, 1H); 1.92 (m, 4H); 2.70 (t, 2H); 2.80 (dd, 1H); 8.81 (d, 1H).

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N-[4-0xo-2-(1H-5-tetrazoly1)-4H-1-benzopyran-8-vll-1-(4-phenylbutyl)-3-methylindole-5-carboxamide 17A Methyl indole-5-carboxylate Example 17:

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the from indole-5-carboxylic acid, Following the process described in title compound was prepared (92% yield). (point A), starting

3.98 (s, 3H); 6.64 (t,

1H N.M.R. (300 MHz, CDC13) & ppm:

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1H); 8.43 7.91 (dd, 7.40 (d, 1H); 1H) 8.53 (broad s, 7.26 (t, 1H);

17B Methyl 3-Formylindole-5-carboxylate

E), starting from methyl indole-5-carboxylate, the title (point Following the process described in example 1 prepared (90% yield). Mas compound

ហ

(q′ 6.63 1H); 10.00 3H); 8 ppm: 3.90 (s, 8.80 (s, 1H); 7.90 (d, 1H); 8.45 (s, 1H); (300 MHz, DMSO) 12.46 (broad s, 1H). 1H N.M.R. 1H);

1-(4-phenylbutyl)-3-formylindole-5-carboxy-Methyl 170 10

late

(2.234 g, 11.0 mmol) and potassium tert-butoxide (1.259 11.2 mmol) in dry N, N-dimethylformamide (50 ml) was methyl 3-formylindole-5-carboxylate g, 11.2 mmol) between 78 for pressure, the resulting residue was partitioned was evaporated off under temperature added with 1-bromo-4-phenylbutane (2.385 TOOL stirring at solvent solution of left under After that the

15

was extracted with chloroform a NaCl saturated solution (50 ml) and chloroform (50 ml) column, obtained which 2.847 g of the title compound (87% yield). the silica gel with n-hexane:ethyl acetate, 70:30, off evaporating purified by chromatography through a crude was and W reduced pressure, phase drying and the aqueous (3x50 ml). After obtaining eluting

20

É 1.91 7.11 7.70 2H); 2H); 1H); É (t, 7.33 (d, 9.98 (s, 1.66 4.16 (300 MHz, CDCl₃) 5 ppm: 3H); 2H); 8.99 (s, 1H); 3.93 (8, 7.25 (d, (dd, 1H); 2H); 1H); (m) (t, 7.19 2.64 8.01 N. M. W.

17D Methyl 1-(4-phenylbutyl)-3-methylindole-5-carboxyla-30

9 53

zinc with cyanoborohydride under stirring at 85°C for 1.5 h. After that the mixture solution of methyl 1-(4-phenylbutyl)-3-formylindichloromethane (200 ml). The solvent was evaporated of feluting with n-hexane:ethyl acetate, 98:2, thereby purified by chromatography through a silica gel column, under reduced pressure and the resulting crude solid dichloromethane (15 ml) was added successively recovering 459 mg of the title compound (80% yield). mixture was filtered through celite, washing the 2.69 mmol) and sodium (843 mg, 13.41 mmol). The resulting mg, 1.79 009) dole-5-carboxylate iodide (857 mg,

M

0 H 1H N.M.R. (300 MHz, CDCl_S) 5 ppm: 1.59 (m, 2H); 1.80 (m, 2H); 2.32 (s, 3H); 2.58 (t, 2H); 3.91 (s, 3H); 4.00 (t, 2H); 6.84 (£, 1H); 7.08 (d, 2H); 7.17 (m, 1H); 7.20-7.27 (m, 3H); 7.87 (dd, 1H); 8.34 (d, 1H).

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17E 1-(4-Phenylbutyl)-3-methylindole-5-carboxylic acid

Following the process described in example 6 (point E), starting from methyl 1-(4-phenylbutyl)-3-methyl-indole-5-carboxylate, the title compound was prepared (quantitative yield).

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¹H N.M.R. (300 MHz, CDCl₃) & Ppm: 1.60 (m, 2H); 1.80 (m, 2H); 2.34 (s, 3H); 2.59 (t, 2H); 4.02 (t, 2H); 6.86 (s, 1H); 7.10 (d, 2H); 7.18 (d, 1H); 7.22-7.26 (m, 3H); 7.97 (dd, 1H); 8.45 (d, 1H).

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17F N-[4-0x0-2-(1H-5-tetrazolvl)-4H-1-benzopyran-8-vll-1-(4-phenylbutyl)-3-methylindole-5-carboxamide

Following the process described in example 1 (point K), starting from 1-(4-phenylbutyl)-3-methylindole-5-carboxylic acid and 8-amino-4-oxo-2-(5-1H-tetrazolyl)-4H-1-benzopyran, the title compound was prepared as a

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yellow solid with melting point 186°-187°C, which was purified by crystallization in methanol (54% yield).

10.05 2H); 1.78 (d, 1H); (s, 3H); 2.59 (t, 2H); 4.21 (t, 2H); 2H); 1.53 (m, 8.33 (s, 1H); 8.38 3H); 7.57 (m, CDC13) 6 ppm: (sc, 7.23-7.29 (dd, 1H); ¹H N.M.R. (300 MHz, 2.35 4H); 8.87 2H);

Example 18: 8-[[4-(4-Phenylbutoxy)phenyllmethyloxy]-4oxo-4H-1-benzopyran-2-carboxylic acid

10 18A Methyl 4-(4-phenylbutoxy)benzoate

and diethyl resulting stirring at room temperature for successively sodium bicarbonate and and methyl 4-hydroxybenzoate (3 g, mmo1) (500 ml) with 0°C. After that The mmol) in ml, 19.7 filtrate was washed mmol). added ether 9, 29.6 29.6 Was (3.04 36 h, then was added with ethyl 0.2M hydrochloric acid, 5% to crystallize for 24 hours at TH ml) triphenylphosphine (7.74 4-phenylbutanol (4.65 (110 left under filtered and the of tetrahydrofuran azodicarboxylate mixture mixture was mmol), with

4

pressure, a residue drying and compound (70% with solution. After increasing of the title À eluting purified reduced column, or O 3.856 g solvent under mixtures saturated WAS silica gel obtained which recovering chloride ether:chloroform removing the ಗ

23

yield). ¹H N.M.R. (300 MHz, CDCl₃) 5 ppm: 1.82 (m, 4H); 2.69 (t, 2H); 3.87 (s, 3H); 4.00 (t, 2H); 6.88 (d, 2H); 7.18-7.31

18B 4-(4-Phenylbutoxy)benzoic acid

2H).

7.98 (d,

5H);

76

Following the process described in example 10 (point B), starting from methyl 4-(4-phenylbutoxy)benzoate, the title compound was prepared which was purified by digestion in ethyl ether (92% yield).

1H N.M.R. (300 MHz, CD₃0D) & ppm: 1.81 (m, 4H); 2.68 (t, 2H); 4.01 (t, 2H); 6.90 (d, 2H); 7.16-7.31 (sc, 5H); 7.97 (d, 2H).

S

18C 4-(4-Phenylbutoxy)benzyl alcohol

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mg, phenylbutoxy)benzoic acid (1.03 g, 3.81 mmol) in 20 ml dry ethyl ether. The mixture was left under stirring atmosphere with a solution of 4-(4slowly with a NaCl saturated solution in water (80 ml), the two phases were separated and the aqueous one was ethyl acetate (3x50 ml). The organic The digestion extracts were evaporated under reduced to obtain a crude, which was digested with ethyl ether. compound (57 suspension of lithium aluminium hydride (309 evaporated mJ) Was mmol) in anhydrous tetrahydrofuran (65 that extracts were dried and the solvent was after pressure to obtain 556 mg of the title at room temperature for 2 hours, added under inert extracted with

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18D 4-(4-Phenylbutoxy)benzyl chloride

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A solution of 4-(4-phenylbutoxy)benzyl alcohol (556 mg, 2.17 mmol) in chloroform (10 ml) was added with thionyl chloride (0.288 ml) and left under stirring at room temperature for 24 h, then evaporated to dryness under reduced pressure to obtain 595 mg of the title

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98 compound (quantitative yield).

lH N.M.R. (300 MHz, CDCl₃) & ppm: 1.76 (m, 4H); 2.64 (t, 2H); 3.89 (t, 2H); 4.49 (s, 2H); 6.81 (d, 2H); 7.13-7.28 (sc, 7H).

18E 2-(2.3-Dimethoxyphenyl)ethan-2-ol

S

with added at 0°C an ammonium chloride added with 0°C for 0.5 2,3-dimethoxybenzaldehyde (10.0 aqueous phase compound methylmagnesium bromide reduced Kas title ether (35 ml) and left under stirring at Were MAS mil) the under Afterwards the reaction mixture ether and extracts (100 the solution, extracting g of off ethyl ether organic diphasic mixture of ethyl evaporated obtaining 10.06 solution of of The dry solution mmol) in ethyl ether. solvent was a 3M saturated thereby yield).

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1H N.M.R. (300 MHz, CDCl₃) & ppm: 1.45 (d, 3H); 3.02
(broad s, 1H); 3.83 (s, 3H); 3.84 (s, 3H); 5.12 (m, 1H);
6.81 (dd, 1H); 6.96-7.06 (sc, 2H).

20 18F 2'.3'-Dimethoxyacetophenone

55.3 mmol) and left under stirring at room temperature potassium which was purified by distillation under high vacuum. At A solution of potassium dichromate (24.76 g), water extracted with chloride 85.0, 2-(2,3-dimethoxyphenyl)ethan-2-ol (10.06 ml) o t a sodium acid (12 S S temperature obtain solvent ethyl ether and washed successively with Was reduced pressure to and with sulfuric 15 min. After that the mixture The at saturated solution (1x100 ml). carbonate solution (2x150 ml) torr and concentrated 0.3 evaporated under and a pressure of added with for

66

.47 g of the title compound distiled (65% yield).

LH N.M.R. (300 MHz, CDCl₃) & ppm: 2.62 (s, 3H); 3.88 (s, 3H); 3.90 (s, 3H); 7.05-7.10 (sc, 2H); 7.21 (dd, 1H).

18G 2'.3'-Dihydroxyacetophenone

S

at 2.5 hours at room temperature, then מ dichloromethane (68 ml). The mixture was left to cool, solvent was evaporated by of (4.85)ethyl acetate (250 ml), washed with added residue purified solution 3.10 stirring the title compound as a yellow solid (76% yield). of 2',3'-dimethoxyacetophenone thereby obtaining Was dryness. The Kas dichloromethane (100 ml) tribromide under which added with methanol (70 ml), left $NaHCO_3$ (1x30 ml), dried and the thereafter evaporated to a 1M boron crude crystallization in methanol, ಥ for obtain keeping stirring solution 26.9 mmol) in -70°C with dissolved in to

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1H N.M.R. (300 MHz, CDCl₃) 6 ppm: 2.61 (s, 3H); 7.05-6.77 (t, 1H); 7.02 (dd, 1H); 7.36 (dd, 1H).

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18H Ethyl 8-hydroxy-4-oxo-4H-1-benzopyran-2-carboxylate

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Following the process described in example 1 (point A), starting from 2',3'-dihydroxyacetophenone, the title compound was prepared (83% yield).

1H N.M.R. (300 MHz, CDCl₃) & Ppm: 1.47 (t, 3H); 4.52 (q, 2H); 7.10 (s, 1H); 7.30 (m, 2H); 7.61 (dd, 1H). 181 Ethyl 8-[[4-(4-phenylbutoxy)phenyl]methyloxy]-4-oxo-48-1-benzopyran-2-carboxylate

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A solution of potassium carbonate (330 mg, 2.39 mmol) in dry N,N-dimethylformamide (15 ml) was added with ethyl 8-hydroxy-4-oxo-4H-1-benzopyran-2-carboxylate (520 mg, 2.39 mmol) stirring at room temperature for 10 min. After that the reaction mixture was added with 4-

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60°C for 18 h, subsequently was off 7:3, recovering ether 2.17 mmol) residue which solvent was evaporated ethy1 silica with chloride (595 mg, 740 mg of the title compound (66% yield). ether:chloroform, extracted ι¢ Ø obtain purified by chromatography through m1), reduced pressure, to the at eluting with petroleum (4-phenylbutoxy)benzyl (25 dried and stirring water m1), with under

n

1H N.M.R. (300 MHz, CDCl₃) & ppm: 1.40 (t, 3H); 1.80 (m, 4H); 2.66 (t, 2H); 3.95 (t, 2H); 4.41 (q, 2H); 5.16 (s, 2H); 6.89 (d, 2H); 7.09 (s, 1H); 7.16-7.29 (sc, 7H); 7.40 (d, 2H); 7.71 (dd, 1H).

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18J 8-[[4-(4-Phenylbutoxy)phenyl]methyloxy]-4-0xo-4H-1-benzopyran-2-carboxylic acid

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Following the process described in example 1 (point M), starting from ethyl 8-[[4-(4-phenylbutoxy)phenyl]methyloxy]-4-oxo-4*H*-1-benzopyran-2-carboxylate, the title compound was prepared as a slightly yellowish semisolid (78% yield).

1H N.M.R. (300 MHz, CD₃OD) 6 ppm: 1.78 (m, 4H); 2.66
(broad t, 2H); 3.95 (broad t, 2H); 5.20 (s, 2H); 6.87
(d, 2H); 7.10 (s, 1H); 7.14-7.34 (sc, 7H); 7.40 (d, 2H);
7.69 (dd, 1H).

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Example 19: 8-[[4-(4-Phenylbutoxy)phenyl]sulfonylaminol-

25 4-0x0-4H-1-benzopyran-2-carboxylic acid

19A N-(3-Acetyl-2-hydroxyphenyl)-4-methoxybenzenesulfonamide A solution of 3'-amino-2'-hydroxyacetophenone hydrobromide (1.282 g, 5.52 mmol) in pyridine (25 ml) was added at 0°C with 4-methoxybenzenesulfonyl chloride (1.18 g, 5.71 mmol) dissolved in the minimum amount of

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pyridine and the mixture was left at room temperature for 18 h. Afterwards it was evaporated to dryness, redissolved in dichloromethane, washed with 1M HCl, dried and the solvent was evaporated off under reduced pressure, thereby obtaining 1.479 g of the title compound (81% yield).

S

1H N.M.R. (300 MHz, CDCl₃) & Ppm: 2.58 (s, 3H); 3.80 (s, 3H); 6.85 (d, 2H); 6.86 (t, 1H); 7.11 (s, 1H); 7.45 (d, 1H); 7.72 (d, 2H); 7.77 (d, 1H); 12.59 (s, 1H). 10 19B Ethyl 8-(4-methoxyphenyl)sulfonylaminol-4-oxo-4H-1-benzopyran-2-carboxylate

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Following the process described in example 1 (point A), starting from N-(3-acetyl-2-hydroxyphenyl)-4-metho-xybenzenesulfonamide and diethyl oxalate, the title compound was prepared, which was purified by chromatography through a silica gel column, eluting with petroleum ether:chloroform 4:6 (90% yield).

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1H N.M.R. (300 MHz, CDCl3) & Ppm: 1.43 (t, 3H); 3.74 (s, 3H); 4.45 (q, 2H); 6.77 (d, 2H); 6.99 (s, 1H); 7.34 (dd, 1H); 7.71 (d, 2H); 7.80 (dd, 1H); 7.88 (d, 1H); 8.66 (s,

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19C Ethyl 8-[(4-hydroxyphenyl)sulfonylamino)]-4-oxo-4H-1-benzopyran-2-carboxylate

Following the process described in example 18 (point G), starting from ethyl 8-(4-methoxyphenyl)sulfonylamino]-4-oxo-4H-1-benzopyran-2-carboxylate, the title compound was prepared, which was purified by chromatography through a silica gel column, eluting with petroleum ether:chloroform, 25:75 (67% yield).

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30 ¹H N.M.R. (300 MHz, CDCl₃) 8 ppm: 1.43 (t, 3H); 4.47 (q, 2H); 6.80 (d, 2H); 6.99 (s, 1H); 7.24 (s, 1H); 7.38 (t,

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1H);

1H).

19D 8-[[4-(4-Phenylbutoxy)phenyl]sulfonylamino]-4-oxo-4H-1-benzopyran-2-carboxylic_acid

- methoxide solution in methanol (0.194 ml, 1.04 mmol) and 5.3M sodium ethyl acetate (3x25 ml), washed with 0.2M HCl, dried and 8-[(4-hydroxyphenyl)sulfonylthereby obtaining 70 mg chloroform:methanol 1-bromo-4-N Subsequently silica for 20°C partitioned at 50°C 0.26 mmol), stirring at with ια obtain a ų amino)]-4-oxo-4H-1-benzopyran-2-carboxylate with chromatography through acetate, 1:1, 18 h. dryness, added stirring added of to at room temperature for with mixtures mixtures of increasing polarity, off, , 0.0 Was mixture was left under to was evaporated ethy1 in DMF (3 ml) at evaporated water:ethyl , gm of cooled purified by column, eluting phenylbutane (57 solution mixture was mixture of solvent 0.26 mmol) was h. and the
- 1H); : mdd 2H); 7.42 (t, ထ í, CD₃OD-CDCl₃ mixtures) (broad 7.14-725 (sc, SH); 7.68 (d, 2H); 7.87 (d, 1H); 7.97 (d, 1H) t, 2H); 3.95 (s, 1H); 2.65 (broad N.M.R. (300 MHz, 6.99 4H); 2H);

the title product (54% yield).

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Example 20: 4-0xo-8-f(E)-2-f4-(4-phenylbutoxy)-phenyll-ethen-1-yll-4H-1-benzopyran-2-carboxylic acid
20A 2'-Hydroxy-3'-iodoacetophenone

acid ပ ပ mmol) A suspension of 3'-amino-2'-hydroxyacetophenone hy ml) at concentrated sulfuric 11.3 (10 Ö mmol) in water (0.783)nitrite with drobromide (2.5 g, 10.8 successively sodium and added 30

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the time the resulting residue was purified by column organic phase ether:chloroform, Copper powder (11 mg) was added in a few minutes and and solution potassium iodide (2.2 g) in water (2 ml) cooled at and the mixture was compound room temperature, was washed with a 5% sodium thiosulfate solution, After under added at 75°C for 2 h. After this ø min. extracted with chloroform (3x50 ml), the Kas title off onto with petroleum sulfuric acid (0.2 ml) 20 of evaporated mixture was poured D for was left to cool at mI) 6:4, thereby recovering 1.95 ပ • dissolved in water (1.5 solvent was eluting at left stirring chromatography The concentrated Was resulting pressure. the mixture

10

S

¹H N.M.R. (300 MHz, CDCl₃) 6 ppm: 2.64 (s, 3H); 7.71 (d, 1H); 7.90 (d, 1H), 13.15 (s, 1H).

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20B 4-(4-Phenylbutoxy)benzaldehyde

(63% starting from 4-hydroxybenzaldehyde and example phenyl-1-butanol, the title compound was prepared described in process the Following (Point A),

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Ţ, <u>'</u> 2.66 7.78 4H); 5H); ¹H N.M.R. (300 MHz, CDCl₃) & ppm: 1.80 (m, 6.93 (d, 2H); 7.16 (sc, 2H); 4.00 (t, 2H); 9.83 (s, 1H) 2H);

20C 4-(4-Phenylbutoxy)styrene

25

1.6M butyl lithium solution in hexane (8.69 ml) and the methyltriphenylphosphonium bromide mixture was left under stirring at 0°C for 2 h. After ml) at 0°C and under inert atmosphere was added with tetrahydrofuran g, 13.9 mmol) in anhydrous ¥,0 solution

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and organic the solvents were evaporated off mI) 4-(4-phenylbutoxy)benzaldehyde compound (62% yield) (20 The resulting crude was column, 95:5, carefully added with water 1 al) stirring at ether, (10 ether (4x50 silica tetrahydrofuran g of the title ether:ethyl ៧ The the mixture was left under through dried and pressure. ethy1 of by chromatography i, solution petroleum with then recovering 4.20 mmol) extracts were reduced extracted 9.84

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5,58 4H); 1H); (ď, 1.78 (m, 5.10 2H); 2H); : mdd (ď, (broad t, 6.82 CDC13) 6 1H); MHZ, 3.95 (dd, (300 2H); 6.64 1H N. M. R. 1H); (ď,

0

3'-[(E)-2-[4-(4-Phenylbutoxy)phenyllethen-1-y1]-2' hydroxyacetophenone 200

₩

the palladium resulting ether, compound (70% yield). 6.85 acetonitrile (15 2'-hydroxy-3'-iodoacetophenone (612 mg, extracted solvents ether:ethyl residue was purified by chromatography through 4H); 2H); 24 h. (sc, 7H); 7.45 3.01 mmol), 4-(4-phenylbutoxy)styrene 8 ppm: 1.79 (m, ml), the under reduced pressure. for (broad with petroleum and 0.06 mmol) in (15 stirring at 100°C 633 g of the title ml, 3.95 dried 7.08-7.36 water mmol), triethylamine (0.408 CDC13) 2H); ml), with acetate (14 mg, column, eluting (broad t, (t, 1H); (300 MHz, (4x30added off left under recovering mixture ether Was 2.92 mmol), evaporated 6.86 2.68 ¹H N.M.R. mixture (II)

25

7.73 (dd, 1H), 12.51 (s, 1H). (dd, 1H);

105

20E Ethvl 4-oxo-8-[(E)-2-[4-(4-phenylbutoxy)phenyll-ethen-1-yll-4H-1-benzopyran-2-carboxylate

Following the process described in example 1 (point A), starting from 3'-[(E)-2-[4-(4-phenylbutoxy)phenyl]-ethen-1-yl]-2'-hydroxyacetophenone and diethyl oxalate, the title compound was prepared, which was purified by chromatography through a silica gel column, eluting with petroleum ether:chloroform, 6:4 (66% yield).

S

1H N.M.R. (300 MHz, CDCl₃) & ppm: 1.41 (t, 3H); 1.80 (m, 4H); 2.67 (broad t, 2H); 3.95 (broad t, 2H); 4.39 (q, 2H); 6.85 (d, 2H); 7.03 (s, 1H); 7.17-7.32 (sc, 8H); 7.44 (d, 2H); 7.77 (d, 1H); 7.93 (dd, 1H).

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20F 4-0xo-8-[(E)-2-[4-phenylbutoxy)phenyllethen-1-yll-4H-1-benzopyran-2-carboxylic_acid

13

Following the process described in example 1 (point M), starting from ethyl 4-0x0-8-[(B)-2-[4-(4-phenylbuto-xy)phenyl]ethen-1-yl]-4H-1-benzopyran-2-carboxylate, the title compound was prepared as a yellow solid with melting point 159-161°C (78% yield).

1H N.M.R. (300 MHz, DMSO) & ppm: 1.74 (broad m, 4H);
2.65 (broad t, 2H); 4.03 (broad t, 2H); 6.94 (s, 1H);
6.99 (d, 2H); 7.17-7.32 (sc, 5H); 7.40 (d, 1H); 7.52 (t, 1H); 7.54 (d, 2H); 7.67 (d, 1H); 7.92 (dd, 1H); 8.13 (dd, 1H).

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Example 21: 8-[(E)-2-[4-(4-Phenylbutoxy)phenyllethen-1-yll-4-oxo-2-(5-1H-tetrazolyll-4H-1-benzopyran

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21A 8-[(E)-2-[4-(4-Phenylbutoxy)phenyllethen-1-yll-4-0x0-4H-1-benzopyran-2-carboxamide Following the process described in example 12 (Point A), by aminolysis reaction of ethyl 8-[(E)-2-[4-(4-phenylbutoxy)phenyl]ethen-1-yl]-4-oxo-4H-1-benzopy-

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106 ran-2-carboxylate, the title compound was prepared as a yellow solid (83% yield).

1H N.M.R. (300 MHz, DMSO) & ppm: 1.73 (broad m, 4H);

2.65 (broad t, 2H); 4.03 (broad t, 2H); 6.91 (s, 1H); 6.99 (d, 2H); 7.17-7.32 (sc, 5H); 7.49 (d, 1H); 7.51 (t, 1H); 7.70 (d, 2H); 7.72 (d, 1H); 7.93 (d, 1H); 8.21 (d, 1H); 8.28 (broad s, 1H); 8.53 (broad s, 1H).

21B 8-[(E)-2-[4-Phenylbutoxy)phenyllethen-1-yll-4-oxo-4H-1-benzopyran-2-carbonitrile

Following the process described in example 2 (point D), by reacting 8-[(E)-2-[4-(4-phenylbutoxy)phenyl]-ethen-1-yl]-4-oxo-4H-1-benzopyran-2-carboxamide with phosphorous oxychloride in DMF for 0.5 h at 0°C, the title compound was prepared (97% yield).

1H N.M.R. (300 MHz, CDCl₃) & ppm: 1.80 (broad m, 4H);
2.67 (broad t, 2H); 3.93 (broad t, 2H); 6.70 (s, 1H);
6.85 (d, 2H); 7.08-7.30 (sc, 7H); 7.38 (t, 1H); 7.43 (d, 2H); 7.91 (d, 1H); 7.98 (d, 1H).

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21C 8-[(E)-2-[4-(4-Phenylbutoxy)phenyllethen-1-y1]-2-4-0xo-(5-1H-tetrazolyll-4H-1-benzopyran

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Following the process described in example 7 (point C), starting from 8-[(E)-2-[4-(4-phenylbutoxy)phenyl]-ethen-1-yl]-4-oxo-4H-1-benzopyran-2-carbonitrile, the title compound was prepared as a yellow solid with

melting point 191.4-192.1°C, which was purified by digestion with methanol (95% yield).

1H N.M.R. (300 MHz, DMSO) & ppm: 1.74 (broad m, 4H);

2.66 (broad t, 2H); 4.03 (broad t, 2H); 7.01 (d, 2H); 7.12 (s, 1H); 7.18-7.32 (sc, 5H); 7.53 (t, 1H); 7.61 (s, 2H); 7.65 (d, 2H); 7.95 (dd, 1H); 8.19 (dd, 1H).

Example 22: 8-[(E)-2-[4-[4-(4-Fluorophenyl)-butoxylphen-

07

vllethen-1-vll-4-oxo-4H-1-benzopyran-2-carboxylic acid

22A 4-(4-Fluorophenyl)-1-butanol
A suspension of aluminium trichloride (10.2 g, 76.

L

0.2M 76.5 0.2M HCl (75 ml) and extracted with ethyl acetate (3x100 left under stirring at 0°C for 15 the mixture was added with 3-(4fluorobenzoyl)propionic acid (5 g, 25.5 mmol) stirring The (250 ml) at 0°C was added with slowly with the through saturated solution, dried and Ď The combined organic phases were washed with the title product pressure. resulting residue was purified by chromatography aluminium trichloride (10.2 silica gel column, eluting with hexane:ethyl מ then added the borane-tert-butylamine complex (13.2 reduced g of 20 h, solvents were removed under 8:2, thereby recovering 2.70 colourless oil (63% yield). for in dichloromethane a NaCl minutes. After that and the mixture was temperature and with mmol) HC1

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44 53

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1H N.M.R. (300 MHz, CDCl₃) & ppm: 1.59 (m, 4H); 2.58 (t, 2H); 3.60 (t, 2H); 6.90-7.12 (m, 5H).

22B 4-[4-fluorophenyl)butoxylbenzaldehyde

20

Following the process described in example 18 (Point A), starting from 4-hydroxybenzaldehyde and 4-(4-fluorophenyl)-1-butanol, the title compound was prepared (43% yield).

1H N.M.R. (300 MHz, CDCl₃) & ppm: 1.80 (m, 4H); 2.65 (t, 2H); 4.03 (t, 2H); 6.95 (m, 3H); 7.12 (m, 2H); 7.81 (d, 2H); 9.85 (s, 1H).

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22C 4-[4-[4-Fluorophenyl]butoxylstyrene

Following the process described in example 20 (point C), starting from 4-[4-(4-fluorophenyl)butoxy]-benzaldehyde, the title compound was prepared, which was

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purified chromatographically through a silica gel
column, eluting with petroleum ether:ethyl ether, 98:2
(58% yield).

1H N.M.R. (300 MHz, CDCl₃) & ppm: 1.75 (m, 4H); 2.56 (t, 2H); 3.87 (t, 2H); 5.06 (dd, 1H); 5.56 (dd, 1H); 6.60 (m, 1H); 6.79 (m, 2H); 6.91 (m, 2H); 7.05 (m, 2H); 7.26 (m, 2H).

M

22D 3'-[(K)-2-[4-[4-(4-Fluorophenyl)butoxylphenyllethen-1-yll-2'-hydroxyacetophenone

example 20 (Point D), starting from 4-[4-(4-fluorophenyl)butoxy]eluting 2'-hydroxy-3'-iodoacetophenone, the purified by (70% yield). described in column, compound was prepared, which was petroleum ether:ethyl ether, 95:5 silica gel process Following the through a and graphy

1H N.M.R. (300 MHz, CDCl₃) 6 ppm: 1.78 (m, 4H); 2.63 (t, 2H); 3.95 (t, 2H); 6.84-6.99 (sc, 5H); 7.14 (m, 3H); 7.34 (d, 1H); 7.45 (d, 2H); 7.62 (d, 1H); 7.75 (d, 1H), 12.55 (s, 1H).

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22E Ethyl 8-[(E)-2-[4-[4-[4-fluoropheny]]butoxylphenyl]-ethen-1-yll-4-oxo-4H-1-benzopyran-2-carboxylate

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thyl oxalate, the title compound was prepared, which was 3'-[(E)-2-[4-[4-(4-fluorophenyl)butoco] umn example 1 silica gel xy]phenyl]ethen-1-yl]-2'-hydroxy-acetophenone ether:chloroform, in purified by chromatography through a described Following the process petroleum from with eluting A)

25

1H N.M.R. (300 MHz, CDCl₃) & ppm: 1.42 (t, 3H); 1.79 (m, 30 4H); 2.65 (broad t, 2H); 3.97 (broad t, 2H); 4.42 (q, 2H); 6.87 (d, 2H); 6.95 (t, 2H); 7.05 (s, 1H); 7.13 (t,

109 2H); 7.28 (d, 1H); 7.33 (broad s, 2H); 7.46 (d, 2H); 7.81(d, 1H); 7.97 (d, 1H). 22F 8-[(E)-2-[4-[4-(4-Fluorophenyl)butoxylphenyl]-ethen-1-yl]-4-oxo-4H-1-benzopyran-2-carboxylic acid

G

Following the process described in example 1 (point M), starting from ethyl 8-[(B)-2-[4-[4-(4-fluorophenyl)-butoxy]phenyl]ethen-1-yl]-4-oxo-4<math>H-1-benzopyran-2-carboxylate, the title compound was prepared as a yellow solid with melting point 161-162°C, which was purified by crystallization in methanol (71% yield).

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1H N.M.R. (300 MHz, DMSO) & ppm: 1.73 (m, 4H); 2.65
(broad t, 2H); 4.04 (broad t, 2H); 6.96 (s, 1H); 7.01
(d, 2H); 7.11 (t, 2H); 7.27 (t, 2H); 7.43 (d, 1H); 7.53
(m, 3H); 7.68 (d, 1H); 7.94 (d, 1H); 8.15 (d, 1H).

Example 23: 8-f(E)-2-[4-[4-[4-Fluorophenyl]butoxylphe-nyllethen-1-vll-4-oxo-2-[5-1H-tetrazolyl]-4H-1-benzopy-ran

23A 8-[(E)-2-[4-[4-[4-Fluoropheny]]butoxylphenyllethen-1-yll-4-oxo-4H-1-benzopyran-2-carboxamide

20

Following the process described in example 12 (point A), by aminolysis reaction of ethyl 8-[(E)-2-[4-[4-(4-fluorophenyl)butoxy]phenyl]ethen-1-yl]-4-oxo-4H-1-benzopyran-2-carboxylate, the title compound was prepared as a yellow solid (93% yield).

1H N.M.R. (300 MHz, DMSO) & Ppm: 1.75 (broad m, 4H);
2.67 (broad t, 2H); 4.06 (broad t, 2H); 6.93 (s, 1H);
7.01 (d, 2H); 7.13 (t, 2H); 7.29 (t, 2H); 7.50 (d, 1H);
7.56 (t, 1H); 7.71 (d, 2H); 7.76 (d, 1H); 7.98 (dd, 1H);
8.25 (dd, 1H); 8.28 (broad s, 1H); 8.55 (broad s, 1H).
23B 8-[(E)-2-[4-[4-(4-E]uoropheny])butoxylphenyl]ethen-

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1-vll-4-oxo-4H-1-benzopyran-2-carbonitrile

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Following the process described in example 2 (point D), reacting 8-[(E)-2-[4-[4-(4-fluorophenyl)butoxy]phenyl]ethen-1-yl]-4-oxo-4<math>H-1-benzopyran-2-carboxamide with phosphorous oxychloride in DMF for 0.5 h at 0°C, the

1H N.M.R. (300 MHz, CDCl₃) & ppm: 1.82 (broad m, 4H);
2.68 (broad t, 2H); 4.01 (broad t, 2H); 6.81 (s, 1H);
6.90-7.52 (sc, 11H); 8.02 (t, 2H).

title compound was prepared (95% yield).

S

23C 8-[(E)-2-[4-[4-(4-Fluorophenyl)butoxylphenyll-ethen-1-yll-4-oxo-2-(5-1H-tetrazolyll-4H-1-benzopyran

10

Following the process described in example 7 (point C), starting from 8-[(E)-2-[4-[4-(4-fluorophenyl)buto-xy]phenyl]ethen-1-yl]-4-oxo-4H-1-benzopyran-2-carboni-

trile, the title compound was prepared as a yellow solid with melting point 173.6-174.7°C, which was purified by crystallization in methanol (83% yield).

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4H); 2H); (d, Ë (broad 7.61 7.01 2H); 7.53 (t, 1H); 2H); 1.74 4.04 (broad t, : mdd w ¹H N.M.R. (300 MHz, DMSO) (m, 3H); 7.27 (m, 2H); 2.66 (broad t, 7.13

7.65 (d, 2H); 7.95 (dd, 1H); 8.19 (dd, 1H).

Example 24: 8-[(E)-2-[4-(4-Phenylbutoxy)-2-fluorophenyllethen-1-yll-4-oxo-4H-1-benzopyran-2-carboxylic acid
24A 2-Fluoro-4-hydroxybenzoic acid

20

Following the process described in example 5 (point G). starting from 2-fluoro-2-hydroxybenzonitrile, the title compound was prepared (quantitative yield).

1H. M.R. (300 MHz, CD₃OD) 5 ppm: 6.61 (dd, 1H); 6.69 (dd, 1H); 7.87 (t, 1H), 12.51 (s, 1H).

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30 Following the process described in example 5 (point C), starting from 2-fluoro-4-hydroxybenzoic acid, the

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title compound was prepared (86% yield).

1H .M.R. (300 MHz, CD₃0D) 6 ppm: 3.83 (s, 3H); 6.55 (dd, 1H); 6.65 (dd, 1H); 7.80 (t, 1H), 12.35 (s, 1H).

24C Methyl 4-(4-phenylbutoxy)-2-fluorobenzoate

L(')

4-phenyl-1-butanol, the title compound was ₩ ₩ (point A), starting from methyl 2-fluoro-4-hydroxybenprepared, which was purified by chromatography through a acetate, example eluting with hexane:ethyl in described process column, the 95:5 (97% yield). Following gel zoate and

1H .M.R. (300 MHz, CDCl₃) & ppm: 1.80 (m, 4H); 2.67 (t, 2H); 3.87 (s, 3H); 3.96 (t, 2H); 6.58 (dd, 1H); 6.67 (dd, 1H); 7.17-7.29 (m, 5H); 7.87 (t, 1H).

0

24D 4-(4-Phenylbutoxy)-2-fluorobenzyl alcohol

72

Following the process described in example 1 (point C), starting from methyl 4-(4-phenylbutoxy)-2-fluorobenzoate, the title compound was prepared (quantitative yield).

1H .M.R. (300 MHz, CD₃OD) & ppm: 1.69 (m, 4H); 2.57 (t, 2H); 3.81 (t, 2H); 4.59 (s, 2H); 6.57 (dd, 1H); 6.64 (dd, 1H); 7.09-7.24 (m, 5H); 7.28 (t, 1H).

20

24E 4-(4-Phenylbutoxy)-2-fluorobenzaldehyde

dichloromethane (50 ml) 4-(4-phenylbutoxy)-2-fluorobenzyl on celite, washing chromatography through a silica gel column, eluting with ρχ of the title dichloromethane. After drying and removing mmol), stirring at room temperature for 1 h. After purified Ď added with pyridinium chlorochromate (1.63 1.02 g Mas reaction mixture was filtered dichloromethane, thereby recovering crude g, 5.03 mmol) in resulting O.F solution the alcohol (1.38

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compound (74% yield).

1H .M.R. (300 MHz, CDCl₃) & ppm: 1.83 (m, 4H); 2.69 (t, 2H); 4.01 (t, 2H); 6.57 (dd, 1H); 6.73 (dd, 1H); 7.17-7.31 (m, 5H); 7.79 (t, 1H); 10.18 (s, 1H).

24F 4-(4-Phenylbutoxy)-2-fluorostyrene

S

Following the process described in example 20 (point C), starting from 4-(4-phenylbutoxy)-2-fluorobenzaldehyde and methyl triphenylphosphonium salt, the title compound was prepared, which was purified by chromatography through a silica gel column, eluting with hexane:ethyl acetate, 1:1 (65% yield).

70

1H N.M.R. (300 MHz, CDCl₃) & ppm: 1.78 (m, 4H); 2.66 (t, 2H); 3.90 (t, 2H); 5.21 (dd, 1H); 5.65 (dd, 1H); 6.55 (dd, 1H); 6.62 (dd, 1H); 6.78 (dd, 1H); 7.17-7.31 (m, 5H); 7.35 (t, 1H).

24G 3'-[(E)-2-[4-Phenylbutoxy)-2-fluorophenyllethen1-yll-2'-hydroxyacetophenone

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starting from 4-(4-phenylbutoxy)-2-fluoroexample 2'-hydroxy-3'-iodoacetophenone, the ρλ eluting with purified described in ether:ethyl acetate, 95:5 (67% yield). Was column, which process prepared, chromatography through a Following the compound was styrene and (point D),

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1H N.M.R. (300 MHz, CDCl₃) 6 ppm: 1.78 (m, 4H); 2.59 (s, 3H); 2.66 (t, 2H); 3.91 (t, 2H); 6.56 (dd, 1H); 6.64 (dd, 1H); 6.86 (t, 1H); 7.17-7.30 (m, 6H); 7.40 (d, 1H); 7.53 (t, 1H); 7.59 (dd, 1H); 7.74 (dd, 1H), 12.82 (s, 1H).

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24H Ethyl 8-[(E)-2-[4-(4-phenylbutoxy)-2-fluorophenyll-

ethen-1-yll-4-oxo-4H-1-benzorvran-2-carboxylate Following the process described in example 1 (poin

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A), starting from 3'-[(E)-2-[4-(4-phenylbutoxy)-2-fluorophenyl]ethen-1-yl]-2'-hydroxy-acetophenone and diethyl oxalate, the title compound was prepared (quantitative

1H N.M.R. (300 MHz, CDCl₃) & Ppm: 1.40 (t, 3H); 1.79 (m, 4H); 2.66 (t, 2H); 4.40 (q, 2H); 3.91 (t, 2H); 6.57 (dd, 1H); 6.64 (dd, 1H); 7.02 (s, 1H); 7.17-7.32 (m, 6H); 7.37 (d, 2H); 7.46 (t, 1H); 7.78 (d, 1H); 7.95 (d, 1H).

S

241 8-[(E)-2-[4-(4-Phenylbutoxy)-2-fluorophenyllethen-1-

vll-4-oxo-4H-1-benzopyran-2-carboxylic acid

10

Following the process described in example 1 (point M), starting from ethyl 8-[(E)-2-[4-(4-phenylbutoxy)-2-fluorophenyl] ethen-1-yl]-4-oxo-4*H*-1-benzopyran-2-carbo-xylate, the title compound was prepared as a yellow solid with melting point 73.4-73.5°C, which was purified by crystallization in methanol (52% yield).

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1H N.M.R. (300 MHz, CDCl₃/CD₃OD mixtures) & ppm: 1.81
(broad m, 4H); 2.69 (broad t, 2H); 3.95 (broad t, 2H);
6.60 (d, 1H); 6.69 (d, 1H); 7.17-7.32 (m, 6H); 7.41 (t, 1H); 7.52 (s, 2H); 7.58 (t, 1H); 7.94 (d, 1H); 8.06 (d, 1H);

20

Example 25: 8-f(E)-2-f2-(4'-Fluorobenzyloxymethyl)-2.3-dihydrobenzofuran-5-yllethen-1-yll-4-oxo-4H-1-benzopy-ran-2-carboxylic acid

25A 2-(4'-Fluorobenzyloxymethyl)-5-hydroxymethyl-2,3-di-hydrobenzofuran

25

Following the process described in example 18 (Point C), starting from ethyl 2-(4'-fluorobenzyloxy-methyl)-2,3-dihydrobenzofuran-2-carboxylate (7.00 g, 23.2 mmol), LiAlH₄ (3.51 g, 92.6 mmol) and dry ethyl ether (300 ml), the title compound was prepared (83%)

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yield).

1H N.M.R. (300 MHz, CDCl₃) & ppm: 2.90 (dd, 1H); 3.08 (broad s, 1H); 3.14 (dd, 1H); 3.55 (dd, 1H); 3.61 (dd, 1H); 4.44 (s, 2H); 4.50 (dd, 2H); 4.90 (m, 1H); 6.70 (d, 1H); 25B 2-(4'-Fluorobenzyloxymethyl)-5-formyl-2.3-dihydro-

6.98 (m, 3H); 7.08 (s, 1H); 7.26 (m, 2H).

1H);

S

Following the process described in example 24 (point E), starting from 2-(4'-fluorobenzyloxymethyl)-5-hydroxymethyl-2,3-dihydrobenzofuran, the title compound was prepared (72% yield).

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1H N.M.R. (300 MHz, CDCl₃) 6 ppm: 3.06 (dd, 1H); 3.30 (dd, 1H); 4.56 (d, 2H); 4.44 (s, 2H); 5.09 (m, 1H); 6.89 (d, 1H); 7.01 (t, 2H); 7.27 (m, 2H); 7.67 (d, 1H); 7.71 (s, 1H); 9.82 (s, 1H).

25C 2-(4'-Fluorobenzyloxymethyl)-5-vinil-2.3-dihydrobenzofuran

72

20 prepared, which was purified by chromatography through a from 2-(4'-fluorobenzyloxymethyl)-5example compound in with petroleum formy1-2,3-dihydrobenzofuran, the title described process eluting acetate, 95:5 (58% yield). (point C), starting column, Following the gel

20

1H N.M.R. (300 MHz, CDCl₃) & ppm: 2.98 (dd, 1H); 3.21 (dd, 1H); 4.58 (dd, 1H); 4.66 (dd, 1H); 4.52 (d, 1H); 4.56 (d, 1H); 5.06 (d, 1H); 5.55 (d, 1H); 6.73 (d, 1H); 7.00 (t, 2H); 7.12 (dd, 1H); 7.23-7.29 (m, 3H).

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25D 3'-[(E)-2-[2-(4'-Fluorobenzyloxymethyl)-2.3-dihydro-benzofuran-5-yllethen-1-yll-2'-hydroxyacetophenone

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Following the process described in example 20

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2'-hydroxy-3'compound was prepared, which gel (point D), starting from 2-(4'-fluorobenzyloxymethyl)-5acetate, a silica ether:ethy1 through with petroleum chromatography the title vinil-2,3-dihydrobenzofuran 85:15 (63% yield). iodoacetophenone, purified by column, eluting

ĽΩ

1H); 1H); 6.85 (t, ¹H N.M.R. (300 MHz, CDCl₃) 6 ppm: 2.58 (s, 3H); 4.50 (d, (t, 2H); 7.08 (d, 1H); 7.22-7.32 (m, 4H); 7.57 (d, 1H); 7.70 (d, 1H); 12.88 (s, 1H). 4.56 (d, 1H); 4.96 (m, 1H); 6.76 (d, 1H); 1H); 3.22 (dd, 1H); 3.63 (m, 2H); 1H);

0

8-[(E)-2-[2-(4'-Fluorobenzyloxymethyl)-2.3dihydrobenzofuran-5-yllethen-1-yll-4-oxo-4H-1-benzopy-Ethyl

ran-2-carboxylate

75

starting from 3'-[(E)-2-[2-(4'-fluorobenzyloxymeacetophenone and diethyl oxalate, the title compound was thyl)-2,3-dihydrobenzofuran-5-yl]ethen-1-yl]-2'-hydroxy-Following the process described in example 1 prepared (quantitative yield). A),

2H); 3H); (t, 3H); 7.01 (m, 4.42 (q, (dd, 1H); 7.96 (d, 1H). 4.53 (d, 1H); 4.58 (d, 1H); 6.78 (d, 1H); ¹H N.M.R. (300 MHz, CDCl₃) 8 ppm: 1.43 (dd, 1H); 3.26 (dd, 1H); 3.66 (m, 2H); 7.27-7.38 (m, 7H); 7.81

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25F 8-[(E)-2-[2-(4'-fluorobenzyloxymethyl)-2.3-dihydrobenzofuran-5-vllethen-1-vll-4-oxo-4H-1-benzopyran-2-carboxylic acid

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Following the process described in example 1 (point M), starting from ethyl 8-[(E)-2-[2-(4'-fluorobenzyloxy- $\mathtt{methyl})$ -2,3-dihydrobenzofuran-5-yl]ethen-1-yl]-4-oxo-4Hmelting point title with the a yellow solid 1-benzopyran-2-carboxylate, id so prepared

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With digestion β purified which was ether (53% yield). 205.4°C,

2H); (dd, 7.14 (s, 1H); 7.32 (m, 3H); 7.38-7.45 (m, 4H); 7.92 : mdd 6.79 (d, 1H); 7.03 (t, 4.55 (d, CDC13/CD3OD mixtures) 8 2H); 3.31 (dd, 1H); 3.69 (m, (d, 1H); 5.02 (m, 1H); ¹H N.M.R. (300 MHz, 8.01 (dd, 1H). 1H);

S

8-[(E)-2-[2-(4'-Fluorobenzyloxymethyl)-2.3dihydrobenzofuran-5-yllethen-1-yll-4-oxo-2-(5-1H-tetra-Example 26

zolyl]-4#-1-benzopyran 10

8-[(E)-2-[2-(4'-Fluorobenzyloxymethyl)-2.3-dihydrobenzofuran-5-yllethen-1-yll-4-oxo-4H-1-benzopyran-2-carboxamide

t; example 12 8-[(E)-2-[2a yellow solid (83% yield). (4'-fluorobenzyloxymethyl)-2,3-dihydrobenzofuran-5-yl]ethen-1-yl]-4-oxo-4H-1-benzopyran-2-carboxylate, the ppm: 3.02 (dd, 1H); process described in aminolysis reaction of ethyl ¹H N.M.R. (300 MHz, DMSO) 6 compound was prepared as Following the (point A), by

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5H); 8.28 (dd, 1H); 3.67 (m, 2H); 4.55 (s, 2H); 5.04 (m, 1H); (s, 1H); 7.17 (t, 2H); 7.35-7.53 (m, 8.17 (d, 1H); 7.65-7.72 (m, 2H); 7.94 (d, 1H); 8.53 (broad s, 1H). (d, 1H); 6. 93 (broad s, 1H);

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8-[(E)-2-[2-(4'-Fluorobenzyloxymethyl)-2.3-dihydrobenzofuran-5-vllethen-1-vll-4-oxo-4H-1-benzopyran-2-carbonitrile

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(point 8-[(E)-2-[2-(4'-fluorobenzyloxymethyl)-Following the process described in example 2 2,3-dihydrobenzofuran-5-yl]ethen-1-yl]-4-oxo-4*H*-1reacting

prepared benzopyran-2-carboxamide with phosphorous oxychloride compound was 0°C, the title a tt **,**¤ for 0.5

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(76% yield).

1H N.M.R. (300 MHz, CDCl₃) 6 ppm: 3.06 (dd, 1H); 3.32 (dd, 1H); 3.67 (m, 2H); 4.55 (d, 1H); 4.61 (d, 1H); 5.03 (m, 1H); 6.80 (s, 1H); 6.82 (d, 1H); 7.03 (t, 2H); 7.16 (d, 1H); 7.26-7.33 (m, 4H); 7.42-7.45 (m, 2H); 7.98 (d, 1H); 8.02 (d, 1H).

S

26C 8-[(E)-2-[2-(4'-Fluorobenzyloxymethyl)-2,3-dihydro-benzofuran-5-yllethen-1-yll-4-oxo-2-(5-1#-tetrazolyll-

4H-1-benzopyran

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was crystallized from pentane:chloroform (point 8-[(E)-2-[2-(4'-fluorobenzyloxymea yellow solid with melting point 137.5thyl)-2,3-dihydrobenzofuran-5-yl]ethen-1-yl]-4-oxo-4H-1compound mixtures and recrystallized in benzene (42% yield). Following the process described in example 7 title benzopyran-2-carbonitrile, the from which starting N N 140.8°C, prepared (C)

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1H N.M.R. (300 MHz, DMSO) 6 ppm: 3.05 (dd, 1H); 3.33 (dd, 1H); 3.67 (m, 2H); 4.55 (s, 2H); 5.04 (m, 1H); 6.84 (d, 1H); 7.11 (s, 1H); 7.18 (t, 2H); 7.35-7.40 (m, 2H); 7.45 (d, 1H); 7.52 (t, 1H); 7.54-7.61 (m, 3H); 7.94 (d, 1H); 8.17 (d, 1H).

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Biological activity tests

The antagonistic activity on LTD_4 of the compounds of the present invention is determined by means of an inhibition test of the $[^3\text{H}]\text{-LTD}_4$ receptor binding in guinea-pig lung membranes.

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 $L^{2}H1-LTD_{\underline{4}}$ receptor binding inhibition test in quinea-pig lung membranes

Guinea pig lung membranes, containing the LTD₄ receptors, are purified following the method described by Mong and col. (Mong et al., *Prostaglandins*, 1984, 28.

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different PIPES buffer The reaction mixture is incubated for added glycine, rđ test in are Hd) and 2 量 acid) (150 µg/ml) M Of GBq/mmol) product under cysteine, (piperazine-N, N'-bis (2-ethanesulfonic containing 10 805). These purified membranes 2 mM (4700-6400 concentrations of the 10 mM $MgCl_2$, mixture 30 minutes at 25°C. volume of 310 µl. an incubation [3H]-LTD4

M

The radioligand bound to the membranes is separated at 0°C and free one by dilution with 4 ml washing buffer is determined 0.U of th Lt filters, by means খ্যা buffer washed NaC1) filters are of washing 100 mM filters in the Whatman GP/B (10 mM Tris-HCl (pH 7.4) and 16 ml Harvester. The radioactivity present volume of filtration with Ce11 a total from the Brandel The

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by liquid scintillation.

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determines by means difference tests of $(K_{\underline{1}})$ al., presence competition computational program, which the compound [3H]-LTD4 (Cheng et is defined as the data obtained in the each in of equation specific binding determined binding 1973, 22, 3094). constant of binding Cheng-Prusoff total specific inhibition analyzed by a the The Pharmacol., between the

20

Ki = IC50 / (1 + [L] / Kd)

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compound which the is N S T in $[^3\mathrm{H}]\mathrm{LTD}_4$ free in the test and K_d radioligand, [L] obtained Scatchard analysis. οŧ LTD4 wherein IC_{50} is the concentration the the bound of independent way by means of constant of 508 concentration of dissociation rd displaces

The selected compounds of general formula I show in

	u	ø	ø.	
	test	The	are	
	H.	nX.	spur	
	itic	0.1	compounds	
	inhibition	and		
	TIS.	1000	representative	
On.	binding	between	preser	
119		bet	rel	
	eceptor	(Ki)	some	
	rec	ants	οŧ	
	bed	constan	lues	1e 1
	scri		%	Tab
	de	hibition	vity	n in
	the	inhi	activi	show

120 Table 1	[3H]-LTD4 Receptor binding	inhibition Ki (nM)	145±34	12.0±4	5.6±0.5	2.3±0.2	24.0±3	6.0±2.1	1.88±0.2	1.73±0.2	1.1±0.2	8.0±0.8	1.9±0.04	0.39±0.1	6.3±3	4.2±1.1	102±48	169±24	1200±440	174143	6.0±1.0	6.2±1.3	0.5±0.2	€.0±3	0.39±0.1	22.3±0.1	1.25±0.3	0 46+0 1
	Compound	Example No	ਜ	2	ന	vd*	ស	9	7	ω	თ	10	11	12	13	14	15	16	1.7	18	19	20	21	22	23	24	25	26
				ហ					10					S T					20					25				

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CLAIMS

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1. A compound of formula I,

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wherein:

A is an oxygen or sulfur atom or a methylene group;B can be:

a) a benzofused heterocycle

H 2

wherein:

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the benzofused group, the said substituent a NR5 (C_1-C_4) -alkyl, substituted atom or of substituent containing A when 1- position oxygen or sulfur R⁵ is hydrogen or optionally the being heterocycle; an wherein (S) group ponnoq Þ

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- Z and Y represent two carbon atoms linked together by a single bond or by a double bond;

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- T is a single bond, a methylene group or a

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carbonyl group;

and wherein:

- the substituent containing A is bound to any one of the possible 1-, 2-, 3- or 4- position of the

benzofused heterocycle;

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 the substituent containing C is bound to the 6or 7- position of the benzofused heterocycle;

b) a phenyl group

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wherein the substituent containing C is bound to the phenyl group at the 3-, 4- or 5- position;

- C is a diradical which represents:

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a) when B is a benzofused heterocycle, a $-\text{CONR}^7-$, $-\text{CH}_2\text{NR}^7-$, $-\text{CH}_2\text{O}-$, -CH=CH- group, wherein R⁷ is hydrogen or methyl;

b) when B is a phenyl group, a $-50_2 \rm NR^7-$, $-\rm CH_2^{0-}$, - CH=CH- group, wherein R 7 is hydrogen or methyl;

- D is a 5-tetrazolyl or -COOR 8 group, wherein R 8 is hydrogen, a (c_1-c_4) -alkyl or a phenylalkyl group of less than 10 carbon atoms;

25 - R¹, R², R³, R⁴ and R⁶ are independently hydrogen, halogen, (c_1-c_4) -alkyl, $-0CH_3$ or -0H;

- m and n are integers from 0 to 4;

as well as the solvates and pharmaceutically acceptable salts thereof and all the possible stereoisomers or

2. A compound according to claim 1, wherein R^1 and R^2

mixtures thereof.

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hydrogen, Q S and wherein R8 chlorine dronb, 0 fluorine COORB methyl, ethyl or benzyl 5-tetrazolyl or hydrogen, are

N HO claims 1 o£ wherein B is a benzofused heterocycle, one any A compound according to

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and C is -conR⁷- or -CH=CH-.

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the group, wherein R⁵ wherein R³ substituted m claim hydrogen or methyl and U is a NR⁵ can be to according substituent containing A. methyl or compound hydrogen or

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fluorine, chlorine, methyl according to claim 3, wherein R3 hydrogen, R4 is hydrogen, methoxide and U is oxygen. A compound

of substituent containing C is bound to the 6- position wherein according to claim 3, the central benzofused heterocycle, A compound

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6, wherein T -CH=CH-1- or 2- position of the central benzofused heterocycle. group and the substituent containing A is bound isa Z-X claims 4 and group, a carbonyl to according a single bond or compound ~<

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A compound according to claims 5 and 6, wherein the Substituent containing A is bound to the 2- position of the central benzofused heterocycle.

A compound according to any one of claims wherein m and n are integers from 1 to 2

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N 20 *~ claims of 9110 any a substituted phenyl 124 Ç according compound i) wherein B ∢ 10.

Ŋ

 $-CH_2O-$ or $-SO_2NR^7-$, wherein -CH=CH-D. U and

hydrogen or methyl 10

the are bound to the phenyl wherein compound according to claim 10, group in a respective para position. substituents containing A and C 11. A

A compound according to claims 10 and 11, wherein R6 is hydrogen, fluorine, chlorine, methyl or methoxide

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n is 0, A is oxygen or sulfur and m is 3 to 5.

according to claim 1 selected from the compound following ones: **~**C

8-[2-(benzyloxymethyl)chromane-6-carboxamido]-4-oxo-4<math>H

1-benzopyran-2-carboxylic acid; 20

N-[4-oxo-2-(1H-5-tetrazolyl)-4H-1-benzopyran-8-yl]-2(benzyloxymethyl)chromane-6-carboxamide; 8-[2-(3-phenylpropyl)chromane-6-carboxamido]-4-oxo-4H-1 benzopyran-2-carboxylic acid; N-[4-oxo-2-(1H-5-tetrazolyl)-4H-1-benzopyran-8-yl]-2-(3. phenylpropyl)chromane-6-carboxamide; 23

8-[2-(benzyloxymethyl)benzofuran-5-carboxamido]-4-oxo 4H-1-benzopyran-2-carboxylic 8-(2-benzyloxymethyl-2,3-dihydrobenzofuran-5-carboxami

do)-4-oxo-4H-1-benzopyran-2-carboxylic acid; 30

N-[4-oxo-2-(1H-5-tetrazolyl)-4H-1-benzopyran-8-yl]-2

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benzyloxymethyl-2,3-dihydrobenzofuran-5-carboxamide;

8-[2-(3-phenylpropyl)-2,3-dihydrobenzofuran-5-carboxami-

do]-4-oxo-4H-1-benzopyran-2-carboxylic acid;

N-[4-0xo-2-(1H-5-tetrazoly1)-4H-1-benzopyran-8-y1]-2-(3-1)

5 phenylpropyl)-2,3-dihydrobenzofuran-5-carboxamide;

8-(2-benzylthiomethyl-2,3-dihydrobenzofuran-5-carboxami-

do)-4-0x0-4H-1-benzopyran-2-carboxylic acid;

8-[2-(4'-fluorobenzyloxymethyl)-2,3-dihydrobenzofuran-5-carboxamido]-4-oxo-4H-1-benzopyran-2-carboxylic acid;

10 N-[4-oxo-2-(1H-5-tetrazoly1)-4H-1-benzopyran-8-y1]-2(4'-fluorobenzyloxymethy1)-2,3-dihydrobenzofuran-5-carboxamide;

8-[7-chloro-2-(3-phenylpropyl)-2,3-dihydrobenzofuran-5-carboxamido]-4-oxo-4H-1-benzopyran-2-carboxylic acid;

8-[2-(3-phenylpropyl)-2,3-dihydrobenzofuran-5-carboxamido]-6-fluoro-4-oxo-4H-1-benzopyran-2-carboxylic acid; 8-[4-chloro-2-(3-phenylpropyl)-2,3-dihydrobenzofuran-5-

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carboxamido]-4-oxo-4H-1-benzopyran-2-carboxylic acid;

8-[6-chloro-2-(3-phenylpropyl)-2,3-dihydrobenzofuran-5-carboxamido]-4-oxo-4H-1-benzopyran-2-carboxylic acid;

N-[4-oxo-2-(1H-5-tetrazolyl)-4H-1-benzopyran-8-yl]-1-(4-phenylbutyl)-3-methylindole-5-carboxamide;

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8-[[4-(4-phenylbutoxy)phenyl]methyloxy]-4-oxo-4H-1-ben-zopyran-2-carboxylic acid;

8-[[4-(4-phenylbutoxy)phenyl]sulfonylamino]-4-oxo-4H-1-benzopyran-2-carboxylic acid;

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8-[(E)-2-[4-(4-phenylbutoxy)phenyl]ethen-1-yl]-4-oxo-4H-1-benzopyran-2-carboxylic acid;

8-[(E)-2-[4-(4-phenylbutoxy)phenyl]ethen-1-yl]-4-oxo-2-30 (5-1*H*-tetrazolyl)-4*H*-1-benzopyran;

8-[(E)-2-[4-[4-(4-fluorophenyl)butoxy]phenyl]ethen-1-

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yl]-4-oxo-4H-1-benzopyran-2-carboxylic acid;

8-[(B)-2-[4-[4-[4-fluorophenyl)butoxy]phenyl]ethen-1-

yl]-4-oxo-2-(5-1H-tetrazolyl)-4H-1-benzopyran;

8-[(E)-2-[4-(4-phenylbutoxy)-2-fluorophenyl]ethen-1-yl]

5 4-oxo-4H-1-benzopyran-2-carboxylic acid;

8-[(E)-2-[2-(4'-fluorobenzyloxymethyl)-2,3-dihydroben-zofuran-5-yl]ethen-1-yl]-4-oxo-4H-1-benzopyran-2-carboxylic acid;

8-[(S)-2-[2-(4'-fluorobenzyloxymethyl)-2,3-dihydrobenzo-

10 furan-5-yl]ethen-1-yl]-4-oxo-2-(5-1H-tetrazolyl)-4H-1-

benzopyran;

8-[(E)-2-[4-[4-(4-chlorophenyl)butoxy]phenyl]ethen-1-

Yl]-4-oxo-2-(5-1H-tetrazolyl)-4H-1-benzopyran;

8-[(E)-2-[4-[4-(4-methylphenyl)butoxy]phenyl]ethen-1-

15 yl]-4-oxo-2-(5-1H-tetrazolyl)-4H-1-benzopyran;

8-[(E)-2-[4-[4-(4-methoxyphenyl)butoxy]phenyl]ethen-1yl]-4-oxo-2-(5-1H-tetrazolyl)-4H-1-benzopyran;

8-[(E)-2-[4-[4-[4-(iso-propyl)phenyl]butoxy]phenyl]-

ethen-1-yl]-4-oxo-2-(5-1H-tetrazolyl)-4H-1-benzopyran;

20 8-[(E)-2-[4-[4-[4-(tert-butyl)phenyl]butoxy]phenyl]-

ethen-1-yl]-4-oxo-2-(5-1H-tetrazolyl)-4H-1-benzopyran; 8-[(E)-2-[4-[4-(4-chlorophenyl)propyloxy]phenyl]ethen-1-

yl]-4-oxo-2-(5-1H-tetrazolyl)-4H-1-benzopyran;

8-[(E)-2-[4-[4-(4-fluorophenyl)propyloxy]phenyl]ethen-1-

25 yl]-4-oxo-2-(5-1H-tetrazolyl)-4H-1-benzopyran;

8-[(E)-2-[4-[4-(4-methylphenyl)propyloxylphenyl]ethen-1-

Yl]-4-oxo-2-(5-1H-tetrazolyl)-4H-1-benzopyran;

8-[(E)-2-[4-[4-(4-methoxyphenyl)propyloxy]phenyl]ethen-

1-y1]-4-oxo-2-(5-1H-tetrazoly1)-4H-1-benzopyran;

30 8-[(E)-2-[4-[4-[4-(iso-propyl)phenyl]propyloxy]phenyl]ethen-1-yl]-4-oxo-2-(5-1H-tetrazolyl)-4H-1-benzopyran;

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8-[(E)-2-[4-[4-[4-(tert-butyl)phenyl]propyloxy]phenyl]ethen-1-yl]-4-oxo-2-(5-1H-tetrazolyl)-4H-1-benzopyran.

of claim 1, and the pharmaceutically compounds the process for the preparation of acceptable salts thereof, general formula I **₹**

o.

in which process:

(1)

a) when in general formula I D is $-\cos 8$, a compound of general formula II,

오 (CH₂)_m — A — (CH₂)_n — B-

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commercial the n have ៧ with and reacted ≡ ບ` II Ä meanings, R2, wherein \mathbb{R}^1 , mentioned

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above

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III,

compound

III

of obtain exception to with the base, rd the residue R⁸ of presence the in compound IV, wherein R9 hydrogen,

25

COOR E O (CH₂)_m—A — (CH₂)_n —B -

ì

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obtain 40 treatment acid 128 ממ to subjected compound V, which is

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converted into I by cleavage of which coincides with I wherein D is COOR8 or, when D group through alkali hydrolysis; Ω Γ∙ COOH in formula I, the R9 10

a 5-tetrazolyl group, S. Ω Н b) when in general formula a compound of formula VI,

above 40 azide the sodium and n have with reacted E ບັ m : |obtain a compound VII wherein R^1 , R^2 , A, mentioned meanings,

IA

VII

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129 which coincides with I wherein D is the 5-tetrazolyl group; c) alternatively, when in general formula I C is $-co-n r^7$, then a compound VIII,

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VIII

wherein \mathbb{R}^1 , A, B, m and n have the above mentioned meanings, is reacted with a compound IX,

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IX

in L wherein \mathbb{R}^2 and \mathbb{R}^7 have the above mentioned meanings and the compound carboxyreacting a base, to obtain when D carried conventional processes, then suitable or, chloride of in I being is COOH, then E contains a it with compound IX in the presence of group D reaction a compound of formula X, preparing the acid can be equivalent to the the group, VIII according to protecting previously formula I thereby

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×

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which coincides with I, wherein C is $-\text{CONR}^7-$ or is converted in I, wherein C is $-\text{CONR}^7-$, removing any COOH-protecting group present in E;

d) when in general formula I C is $-\text{CH}_2\text{O-}$, then a compound of formula XI,

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XI

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B the above mentioned bromine atom or reacted 1.0 m and n have chlorine or sulfonate group, Ø m 13 arylmeanings and X Ž compound XII, wherein R1, or

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XII

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wherein \mathbb{R}^2 and \mathbb{E} have the above mentioned meanings, in the presence of a base, to obtain a compound of formula XIII.

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XIII

which coincides with I, wherein C is $-\text{CH}_2\text{O}-$ or is converted into I wherein C is $-\text{CH}_2\text{O}-$ removing any COOH-protecting groups present in E;

e) when in formula I C is $- {\rm SO}_2 {\rm NR}^7 -$ and A is oxygen or sulfur, then a compound XIV,

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XIV

wherein \mathbb{R}^2 , \mathbb{R}^7 , \mathbb{B} , \mathbb{E} and \mathbb{n} have the above mentioned meanings and A is an oxygen or sulfur atom, is reacted with a compound $\mathbf{X}\mathbf{V}$,

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wherein \mathbb{R}^1 , X and m have the above mentioned meanings, in the presence of a base to obtain a compound $\mathbf{x}\mathbf{v}\mathbf{I}$,

X

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XVI

30 which coincides with I, wherein C is $-\mathrm{SO}_2\mathrm{NR}^7-$ and A is oxygen or sulfur, or is converted into I, wherein C is

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 $-50_2 \mathrm{NR}^7-$ and A is oxygen or sulfur, removing any COOH-protecting groups present in E;

- f) and, if necessary, the compound of formula I is
 - converted into the desired salt, by treatment with a 5 base or a suitable ion exchanger according to conventional methods.
- 15. The use of a compound of any one of claims 1 to 12 in the preparation of a medicament for the therapeutical treatment of leukotriene-mediated diseases.
- 16. The use according to claim 14, wherein the leukotriene-mediated diseases are of inflammatory or allergic type.

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17. The use according to claim 15, wherein the inflammatory or allergic diseases are: bronchial asthma, allergic rhinitis, allergic conjunctivitis, rheumatoid arthritis, osteoarthritis, tendinitis, bursitis or psoriasis.

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18. The use according to claim 14, wherein the leukotriene-mediated diseases are of cardiovascular

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19. The use according to claim 17, wherein the diseases of cardiovascular type are: cardiac ischemia, cardiac infarction, coronary spasm, cardiac anaphylaxis, cerebral oedema or endotoxic shock.

INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER IPC 6 C07D311/58 C07D311/24 C	C07D405/04 C07D407/12 C0	P 97/01418 C07D405/14
	on and IPC	
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 6 CO7D	by classification symbols)	
Documentation searched other than minimum documentation to the	documentation to the extent that such documents are included in the fields	s scarched
Electronic data base consulted during the international search (name of data base and,	ne of data base and, where practical, search terms used)	4)
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Citation of document, with indecation, where appropriate, of the relevant passages	sate, of the relevant passages	Relevant to claim No.
CHEMICAL ABSTRACTS, vol. 1: 1991 Columbus, Ohio, US; abstract no. 182817v, page 874; column 2; XP002036210 see abstract & JP 00 395 144 A (ONO PHAIR	. 115, no. 17,	1-3,
documents are listed in the continuation of box C.	Patent family members are listed	in annex.
Special categories of cited documents: A document defining the general state of the art which is not considered to be of particular relevance earlier document but published on or after the international filing date document which may throw doubts on priority daim(s) or which is cited to enablish the publication date of another citation or other special reason (as specified) document referring to an oral disclosure, use, exhibition or	T later document published after the international filing date or priority date and not in conflict with the application but cled to understand the principle or theory underlying the invention. X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an invention deanned be considered to involve an inventive step when the	ternational filing date with the application but theory underlying the c darmed invention X be considered to tocument is taken alone c daimed invention nventive step when the
other means document published prior to the international filing date but later than the priority date claimed	ments, such combination being obvious to a in the art. A. document member of the same patent family	nore other such docu- ous to a person skilled it family
ace of the actual completion of the international search 28 July 1997	Date of mailing of the international search report 0 4, 08, 37	grah report
Uling address of the ISA European Patent Office, P.B. 5818 Patendaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo ni, Fax: (+31-70) 340-3016	Authorized officer Francoic	